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ACTIVE IMMUNIZATION AGAINST PERTUSSIS

FINAL REPORT ON THE CLEVELAND IMMUNIZATIONS OF 1934-1935

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Between May 27, 1934, and July 30, 1935, 483 children of Cleveland from 6 to 15 months of age were given pertussis vaccine prepared from strains of Haemophilus pertussis recently isolated and proved to be in phase I of Leslie and Gardner.[1] The children were selected from the active registers of five child welfare stations of the Cleveland Division of Health. As a control group 496 children comparable in age and other pertinent characteristics were selected from the same sources.

METHODS

To insure reasonably complete and equivalent registration of cases for each group, reports of pertussis to the Division of Health were scrutinized currently, but major emphasis was placed on an independent system of notification. To the age of 15 months, the children of both groups were kept under observation by the nurses of the child welfare stations, those who failed to attend during any four week period being visited in their homes. After the age of 15 months, the homes were visited at intervals of four weeks by experienced nurses employed

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1. Leslie, P. H., and Gardner, A. D.: The Phases of Haemophilus Pertussis, J. Hyg. **31**:423-434 (July) 1931.

specifically for this purpose. On report of illness suspected to be pertussis in an inoculated or control child, or in any member of the child's family, a visit was made in every instance by the staff epidemiologist and in doubtful cases by a consultant pediatrician. Observation of both groups was continued through Sept. 12, 1937.

A detailed description of organization and methods, with statistics on occurrence of pertussis from the beginning of the study to Sept. 12, 1936, has been published.[2] Attack rates, calculated by a modified life table method, showed approximately the same incidence in each group during this period. Attacks among the inoculated children appeared to have been milder than among the controls, but no definite conclusion was reached. The present report includes an additional year of observation and a more detailed discussion of the relative severity of pertussis as observed in the inoculated and in the control children.

Preparation of Vaccine.[3]—As more promising results have been reported by others, notably by Madsen,[4] Sauer[5] and Kendrick and Eldering,[6] and since no two investigators use exactly the same method in preparing vaccine, certain comments on this point are necessary. Only recently isolated strains of H. pertussis or strains stated to be in phase I were used by those cited. All used Bordet-Gengou medium as a base. Madsen enriched with horse blood to the concentration of 28 per cent; Sauer, with human blood to 16 per cent, and Eldering and Kendrick[7] with sheep blood to 15 per cent; we used human blood to a concentration of from 25 to 35 per cent. Madsen added nutrient agar (Miller[8]); Eldering and Kendrick added 1 per cent proteose peptone, and we used, slightly changed,[9] the modification of Bordet-Gengou medium recommended by Lawson and Mueller.[10]

Further details regarding Madsen's method of preparing pertussis vaccine were given by Miller:[8] "This preparation is made from strains isolated within the three previous weeks (obviously such a polyvalent vaccine can only be prepared at a Cough Plate Diagnostic Station). The strains are kept on Bordet-Gengou medium until inoculated on the 'vaccine medium' described above. The three-day

2. Doull, J. A.; Shibley, G. S., and McClelland, J. E.: Active Immunization Against Whooping Cough, Am. J. Pub. Health **26**:1097-1105 (Nov.) 1936.

3. An interesting, although inconclusive, report on immunization against pertussis by Dr. Morris Siegel has appeared since this article was written (Am. J. Dis. Child. **56**:1294 [Dec.] 1938).

4. Madsen, T.: Vaccination Against Whooping Cough, J. A. M. A. **101**:187-188 (July 15) 1933.

5. (*a*) Sauer, L. W.: Whooping Cough: A Study in Immunization, J. A. M. A. **100**:239-241 (Jan. 28) 1933; (*b*) Immunization with Bacillus Pertussis Vaccine, ibid. **101**:1449-1453 (Nov. 4) 1933; (*c*) The Known and Unknown of Bacillus Pertussis Vaccine, Am. J. Pub. Health **25**:1226-1230 (Nov.) 1935.

6. Kendrick, P., and Eldering, G.: Progress Report on Pertussis Immunization, Am. J. Pub. Health **26**:8-12 (Jan.) 1936.

7. Eldering, G., and Kendrick, P.: Some Practical Considerations in B. Pertussis Vaccine Preparation, Am. J. Pub. Health **26**:506-510 (May) 1936.

8. Miller, J. J., Jr.: Experimental Observations on the Antigenic Potency of H. Pertussis Extracts, J. Immunol. **26**:247-265 (April) 1934.

9. Sterilization for twenty minutes at 15 pounds of pressure at 121 C. instead of fractional sterilization at 100 C.

10. Lawson, G. M., and Mueller, M.: The Bacteriology of Whooping Cough, J. A. M. A. **89**:275-279 (July 23) 1927.

growth on this latter medium is washed into 1 per cent formalin (0.4 per cent formaldehyde solution) in physiological sodium chloride. After formalization for one week the suspension is centrifuged, resuspended in 0.5 per cent phenol in physiological sodium chloride and standardized to 10,000 million bacteria per cubic centimeter."

Sauer [5a] scraped off the forty-eight hour growth, suspended in a 0.5 per cent phenolized physiologic solution of sodium chloride, refrigerated for a week and diluted with the same solution until 1 cc. contained approximately 10,000,000,000 bacilli.

Kendrick and Eldering [11] washed off the seventy-two hour growth with a physiologic solution of sodium chloride and adjusted the suspension to compare roughly in turbidity with a standard suspension containing 10,000,000,000 bacilli per cubic centimeter. The suspension was centrifuged for an hour or until the supernatant fluid was fairly clear. The supernatant fluid was discarded, and the sediment was resuspended in saline solution containing merthiolate in a dilution of 1:10,000 or 0.5 per cent phenol. The suspension was filtered through cotton and gauze and refrigerated for a week. After the usual tests for sterility the material was again checked against turbidity standards.

Our cultures were grown for forty-eight hours in rectangular bottles with a capacity of either 170 or 240 cc. with surface areas of medium of 45 and 55 sq. cm., respectively. The growth was removed by washing the surface with from 5 to 8 cc. of sterile distilled water, adherent colonies being removed with the point of the pipet. The suspensions were immediately placed in 50 cc. tubes and centrifuged for fifteen to twenty minutes. The centrifugal force varied.[12] The deposit was resuspended in an 0.85 per cent saline solution to which phenol had been added to a concentration of 0.5 per cent. The suspensions were standardized by opacity comparisons to contain approximately 10,000,000,000 organisms of H. pertussis per cubic centimeter, refrigerated for four or five days and tested for sterility.

Our vaccines and those of Madsen and of Kendrick and Eldering are washed once in the sense that they are centrifuged once and resuspended. On the general question of washing, Kendrick and Eldering [11] stated: "The question of *washing the suspension* arises. We have to choose between an unwashed product which carries with it agar, blood and other medium derivatives and a washed vaccine relatively free from them. A washed product surely is preferable if significant antigenic properties are not lost. Since we have found the washed live culture capable of giving a typical skin reaction and a vaccine, even after 3 washings, capable of stimulating Phase I agglutinins rapidly and in high titers, we decided on a *washed product*."

Dosage.—Madsen gave three doses, with a total dose of about 22,000,000,000 organisms, and Kendrick and Eldering gave four doses, with a total of 70,000,000,000. The injections were made subcutaneously by all. Madsen gave the vaccine at intervals of three or four days; the others, at intervals of a week. We followed the method of Sauer, who gave three doses, totaling 80,000,000,000 organisms, subcutaneously, at intervals of a week.

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11. Kendrick, G., and Eldering, G.: Significance of Bacteriological Methods in the Diagnosis and Control of Whooping Cough, Am. J. Pub. Health **26**:147-154 (Feb.) 1935.

12. An international centrifuge, type S. B. I, with a no. 233 head was used. The speed varied, according to the rheostat setting and the number of centrifuge tubes, from 3,100 to 3,500 revolutions per minute.

INCIDENCE OF PERTUSSIS

On reanalysis of the records, certain minor changes from the original report were made. It was ascertained that each of 4 inoculated children who contracted pertussis early in the study received the first dose of vaccine while in the initial stages of the disease. These children were omitted, which reduced the number in the inoculated group to 479. In addition, 5 children are now regarded as having been attacked whose illnesses were previously classified as "suspected pertussis," 2 belonging to the inoculated and 3 to the control group.

For the whole period of 172 weeks, that is, from May 27, 1934, to Sept. 12, 1937, the number of cases reported in each group was as follows: 74 cases in the inoculated group, numbering 479, and 94 cases in the control group, numbering 496.

A more refined analysis of incidence was adopted. For approximately a year from the beginning of the study new children were added at intervals to each group. At various times children were dropped. Those absent for three months or more because of death, removal from the city or other reasons were regarded as taken off the lists on the date of last observation. Such fluctuations in numbers, together with seasonal variations in prevalence of pertussis, demanded comparison of attack rates for relatively short periods. It seemed sufficient to divide the period from May 27, 1934, to Sept. 12, 1937, into fourteen periods of twelve weeks each and one final period of four weeks.

With an adaptation of the life table procedure, the net strength of each group in each period was assumed to be the number registered at the end of the period preceding, minus any who contracted pertussis, plus half of those newly enrolled and minus half of those lost. For example, the number in the control group during the period ending Nov. 10, 1934, was taken as 88. Fifty-three children had been enrolled in the preceding period, but 7 had contracted pertussis and 2 had been lost, which left 44 registered on Aug. 18, 1935. During the period under consideration 98 new children were enrolled, half of whom were added, which made 93; 10 were lost, half of whom were deducted, which made the net strength 88.

Total Experience.—As a preliminary approach, all inoculated children were regarded as enrolled on the date of their first inoculation. This provided the most rigid test, as it allowed no time for immunity to develop. This will be discussed later. Control children were considered as enrolled on the date on which they were first seen, after selection, by the clinic pediatrician. The complete tabulation is given in table 1.

In the whole period, although incidence somewhat favors the inoculated, the difference is not impressive. Inspection shows that from

Feb. 2, 1935, to the end of observation (one hundred and thirty-six weeks) the numbers in each group were approximately the same for each period given in the table, the average being 386 for the inoculated and 379 for the control group. Seventy inoculated and 83 control children were attacked during this period, 18.1 per cent as compared with 21.9 per cent. On an annual basis, this is equivalent to an attack rate of 6.7 per cent for the inoculated children and 8.3 per cent for the controls.

Experience of Those "Completely Immunized" at Least Three Months Previously.—As just noted, with this method inoculated children are considered at risk immediately on receipt of the first dose of vaccine. To allow time for immunity to develop a tabulation was made which is similar to table 1 but in which the inoculated subjects were regarded as enrolled three months after the third inoculation, 60 who had fewer than three doses being excluded. Children of the control group were regarded as enrolled three months later than in the first tabulation. Application of this three month lag shows 57 cases of pertussis in the inoculated and 75 in the control group. The average strength, cases and attack rates for the last one hundred and twelve weeks, that is, from July 20, 1935, to Sept. 12, 1937, are given in table 2.

TABLE 1.—*Incidence of Pertussis in the Control and in the Inoculated Group for Twelve Week Periods* **

12 Week Period, Date of End	Control Group			Inoculated Group		
	Net Strength	Cases of Pertussis	Attack Rate, Percentage	Net Strength	Cases of Pertussis	Attack Rate, Percentage
8/18/34	25	7	28.0	39	1	...
11/10/34	88	0	...	136	1	...
2/ 2/35	193	4	2.1	236	2	0.8
4/27/35	302	3	1.0	328	1	...
7/20/35	401	7	1.7	415	5	1.2
10/12/35	441	10	2.3	442	12	2.7
1/ 4/36	426	4	0.9	424	8	1.9
3/28/36	417	8	1.9	413	6	1.5
6/20/36	406	17	4.2	405	12	3.0
9/12/36	385	14	3.6	389	11	2.9
12/ 5/36	368	5	1.4	373	3	0.8
2/27/37	362	3	0.8	368	2	0.5
5/22/37	358	2	0.6	365	6	1.7
8/14/37	349	8	2.3	356	3	0.8
9/12/37 (4 weeks)	338	2	0.6	351	1	...
		—			—	
Total (172 weeks).....		94			74	

* May 27, 1934, to Sept. 12, 1937.

Exposures in the Home.—In 75 instances in the inoculated group and in the 62 in the control, pertussis is considered to have been introduced into the family by an older child. In 2 of the former cases it was

ascertained that the disease was probably present in the home at the time of the first inoculation. If these children are regarded as not inoculated at the time of exposure, there are 73 instances in which inoculated children were subjected to household exposure. Fifty-six, or 77 per cent, of the children were attacked. In the control group, 62 exposures resulted in 61 attacks. From these figures the most that can be concluded is that under conditions of household exposure the vaccine may have protected 23 per cent of the inoculated children from attack.

The histories of the 17 inoculated children who were exposed in the household and escaped attack have been examined critically. In 1 instance the child, although present in the home at the time of introduction of the disease, was removed for fourteen days after notification. Twelve of the children had atypical coughing and may have had abortive attacks. Strictly speaking, this leaves only 4 who escaped.

TABLE 2.—*Attack Rates for One Hundred and Twelve Weeks* for Children Having Full Dosage at Least Three Months Prior to Enrollment and for a Comparable Group of Uninoculated Children*

Group	Average Number of Subjects	Cases of Pertussis	Attack Rate, Percentage
Inoculated	342	54	15.8
Control	385	70	18.2

* July 20, 1935, to Sept. 12, 1937.

Attack Rate in Relation to Dosage.—Of 419 children receiving full dosage, 38 were lost from observation, leaving 381; among these there occurred 65 cases—an attack rate of 17.1 per cent. Of 60 receiving less than full treatment, 10 were lost, leaving 50. Among these there were 9 cases—an attack rate of 18 per cent.

CLINICAL CHARACTERISTICS

Every effort has been made to apply equivalent diagnostic standards to cases in each group. All children for whom a definite diagnosis was made had paroxysmal coughing; all save 19 in the inoculated and all save 20 in the control series are known to have had characteristic whooping. Cough plates were secured from 60 patients who had been inoculated and from 71 who had not. Of the former group, 41.6 per cent had positive results, and of the latter, 57.7 per cent. When cultures were received within the first two weeks of illness, the percentage of positive results was materially higher but still somewhat lower for the

inoculated subjects, being 60 per cent as compared with 71.4 per cent for the control group.

A summary of the results of cultures for children with and without paroxysmal coughing and whooping is given in table 3.

From table 3 it may be seen that there are included 14 cases [(35 + 14)-(25 + 10)] among the inoculated children and 12 among the controls in which cultures were either negative or not taken and in which characteristic whooping is not known to have occurred. In each of these instances, typical whooping cough was present in the family. In 7 of the inoculated and in 5 of the control series, the child is known to have had, in addition to paroxysmal coughing, relative lymphocytosis, with a count of 60 per cent or higher. The remaining 14 children are considered, in all probability, to have had pertussis. They may be

TABLE 3.—*Cough Plate Cultures for Inoculated and Control Patients With and Without Paroxysmal Coughing and Whooping*

	Inoculated Series		Control Series	
Culture	Total	Number with Cough and Whoop	Total	Number with Cough and Whoop
Positive	25	20	41	33
Negative	35	25	30	22
Not taken	14	10	23	19
Total	74	55	94	74

excluded or allowed to remain; since they are divided equally between the two groups, it seems of little consequence.

The best and perhaps the only reliable index of severity of pertussis is case fatality. No deaths from pertussis occurred in the inoculated group, and only 1 death occurred in the control group. If the cases included are representative of pertussis occurring among children of comparable ages in the general population, a large series would be necessary for one to determine any difference in case fatality between an inoculated and a noninoculated group.

Estimation of Severity from Case Records.—The records have been studied by different persons, working singly and together, in an endeavor to classify the cases according to severity. Various indexes have been used, but there have been so few reliable objective findings that judgment is difficult. Every tabulation, however, has demonstrated a higher proportion of mild attacks in the inoculated than in the control group.

We consider that much closer observation than was possible in the present study should form the basis for a definite conclusion on this

point. Properly kept temperature charts and more accurate information on frequency and duration of whooping and vomiting are required. Records of loss of weight would provide another criterion. With such deficiencies in mind, table 4 is presented for what it is worth. A few unsatisfactory records are omitted from each series.

Leukocyte Counts.—On the average, higher leukocyte counts were found for patients of the control than for those of the inoculated group. This fact may be interpreted as indicating more severe systemic reactions in the former. A summary of the counts, according to week of disease, is given in table 5, the number of patients on which the average is based being given in parentheses.

TABLE 4.—*Classification of Cases According to Severity of Involvement*

Character of Attack	Inoculated Series		Control Series	
	Number	Percentage	Number	Percentage
Mild	41	59.4	30	35.3
Moderate	28	40.6	52	61.2
Severe	0	0.0	3	3.5
Total	69	100.0	85	100.0

TABLE 5.—*Average Leukocyte Counts for Patients of the Control and of the Inoculated Group*

Week of Disease	Mean		Median	
	Control	Inoculated	Control	Inoculated
First	(12) 18,510	(15) 12,590	15,150	11,350
Second	(17) 25,310	(19) 17,850	25,250	15,150
Third	(25) 31,520	(14) 21,270	29,000	18,080
Fourth or later	(21) 19,340	(17) 17,520	18,050	14,250

On the other hand, no significant differences were observed in the lymphocyte counts. In the third week of disease, the median percentage of lymphocytes was 75 for patients in the control and 73 for those in the inoculated series.

SUMMARY

A group of children of ages from 6 to 15 months inoculated with H. pertussis vaccine and observed for one hundred and seventy-two weeks showed an incidence of pertussis only slightly lower than that of a control group composed of comparable children.

Evidence is cited which indicates that the attacks among the inoculated may have been somewhat milder than those occurring in the control group.

EXPERIMENTAL ASTHMA

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Among students of allergy there is a definite cleavage between those who believe in the close parallelism between animal anaphylaxis and human allergy and those who believe that the manifestations of the two conditions, although they may be similar, are mediated by different mechanisms. It has been contended that the anaphylactic state induced in the experimental animal solely through a parenteral introduction of antigen gives rise to an acute violent reaction which is not comparable to the usually sublethal allergic state in a human being. Consequently, in the study of allergic asthma investigators were actuated to devise modifications of the anaphylaxis test which would be more consonant with conditions in the human subject. Liquid or dry antigens were either instilled or insufflated into the nares or were naturally inhaled in the form of a spray.

My associates and I believed that liquid antigens do not provide the ideal medium for such a modification; so in 1927 we [1] devised a technic for sensitizing and shocking animals solely through the inhalation of dry antigenic dust in a natural manner, yet in conformity with the other criteria for true anaphylaxis.

In subsequent studies, we [2] showed that the fetus may be either actively or passively sensitized by the pregnant female's inhalation of the dry antigenic dust; that inhalant sensitization may be accomplished with an antigen other than horse dander, which was used in our original

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These studies were aided by a grant from the American Academy of Arts and Sciences.

From the Departments of Immunology and Pediatrics, New York University College of Medicine.

Read in part at the Sixteenth Annual Meeting of the Association for the Study of Allergy, San Francisco, June 11, 1938.

The experimental work reported in this paper was carried on over a number of years with the assistance of H. L. Gruehl, B.A.

1. Ratner, B.; Jackson, H. C., and Gruehl, H. L.: Respiratory Anaphylaxis: Sensitization, Shock, Bronchial Asthma and Death Induced in a Guinea-Pig by Nasal Inhalation of Dry Horse Dander, Am. J. Dis. Child. **34**:23 (July) 1927.

2. Ratner, B., and Gruehl, H. L.: Transmission of Respiratory Anaphylaxis (Asthma) from Mother to Offspring, J. Exper. Med. **49**:833, 1929.

experiments (castor bean dust [3]); that a guinea pig sensitized by the inhalation of horse dander dust may become sensitive to the homologous horse serum,[4] and that the administration of epinephrine successfully relieves the asthmatic symptoms in the animal.[5] It is not entirely relevant to this study but may be of general interest that we [6] also produced respiratory anaphylaxis in the guinea pig through the ingestion of milk.

The respiratory anaphylaxis thus produced in our experimental animals, we believed, bore sufficient analogy to the asthmatic syndrome in the human being for it to be called experimental asthma.

I. LABORATORY EXPERIMENTS

FACTORS DETERMINING THE ESTABLISHMENT OF SENSITIZATION TO AN INHALED DRY ANTIGEN

In our original studies on experimental asthma we were concerned mainly with proving the thesis that hypersensitiveness can be induced in the guinea pig through the inhalation of dry antigens. Animals were exposed to antigenic dust for one to two hours a day over nineteen days for a total of twenty-five hours. No attempt was made at that time, however, to determine the optimum dose for regular sensitization. This is the subject of our present inquiry.

Methods.—The animals, procured from one dealer, were of uniform age and weighed 300 to 350 Gm. They were exposed to circulating dry horse dander in the dust chamber (fig. 1) for periods varying from a quarter of an hour to five hours. When these periods were longer than one hour, the exposures were made for one hour daily on successive days until the required time was reached. Three weeks after the last exposure each animal received an intravenous injection of 0.5 cc. of horse dander extract in order that we might determine the degree of hypersensitiveness established through inhalation.

Preparation of Horse Dander Dust: As reported previously, horse combings were obtained for us by grooms in a high grade stable. They were collected on large sheets of paper and were free of horse manure and other extraneous matter, with the possible exception of a stray piece of hay or straw.

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3. Ratner, B., and Gruehl, H. L.: Respiratory Anaphylaxis (Asthma) and Ricin Poisoning Induced with Castor Bean Dust, Am. J. Hyg. **10**:236, 1929. Ratner, B.: Dust Hypersensitiveness with Special Reference to Castor Bean, J. Allergy **2**:1, 1930.

4. Ratner, B., and Gruehl, H. L.: Anaphylactic Crossed Relationship Between Horse Dander and Horse Serum, Arch. Path. **8**:635 (Oct.) 1929. Ratner, B.: A Possible Explanation for Horse Serum Anaphylaxis in Man, J. A. M. A. **94**: 2046 (June 28) 1930.

5. Ratner, Jackson and Gruehl.[1] Ratner and Gruehl.[3]

6. Ratner, B., and Gruehl, H. L.: Passage of Native Proteins Through the Normal Gastrointestinal Wall, J. Clin. Investigation **13**:517, 1934.

The mass consisted of the dander, a light gray, sticky powder, intimately mixed with fine hairs. The fat was dissolved with anhydrous ether, and the dander was separated from the hair and grit by decantations onto filter paper. This process was repeated several times until most of the fat and hair were removed. The dander was thoroughly washed with ether until no visible color could be detected in the washings, extracted with a Soxhlet apparatus and finally air dried. The fine gray powder obtained easily passed through a 200 mesh sieve.

The horse dander extract was prepared as follows: The fat-free and hair-free dander was soaked in a hundredth-normal solution of potassium hydroxide (1 Gm. of dust to 100 cc. of solution) at 37.5 C. for an hour and three quarters. The resulting solution was muddy, with a moderate amount of undissolved sediment. It was filtered, centrifuged and refiltered through paper pulp and animal charcoal and finally passed through a sterile Berkefeld N candle or a Seitz filter. The final solution was clear, amber colored and sterile. It gave the various protein

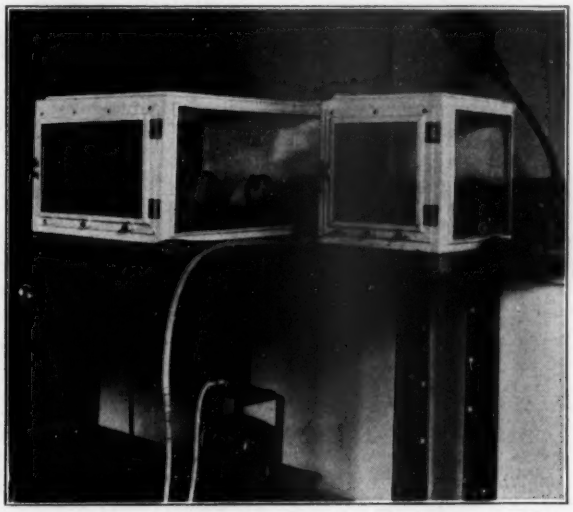

Fig. 1.—Improved inhalation chambers made of enameled metal and glass, the top and three sides being glass. The corners were rounded to obviate collection of dust and to facilitate cleaning. A false wire floor (½ inch [1.27 cm.] mesh) elevated about 2 inches (5 cm.) above the true floor prevented the animals from lying in the dust.

In the experiments a small amount of dust was placed on the true floor. After the false floor was placed in position, the animals were put into the chamber, and the glass door was locked. To circulate the dust, alternating puffs of air were then forced through a hole in the wall between the true and the false floor by means of a tube attached to an electric pump.

With this apparatus we made provision for (1) an unobstructed view of the animals, (2) adequate ventilation and (3) gentle circulation of the dust. A vent was provided at the top of the cage to prevent any increase in air pressure in the chamber.

color reactions and formed a precipitate with mineral acids and alkaloid reagents. Analysis of the nitrogenous content showed 144 mg. of total nitrogen per cubic centimeter, 46 mg. of nonprotein nitrogen and 98 mg. of protein nitrogen. The p_H

was above 8, but whenever the solution was used for intravenous injection the p_H was adjusted to 7.4. We found, as did Longcope, O'Brien and Perlzweig,[7] that the solution becomes more alkaline on standing, so that readjustments had to be made when a given solution was used on more than one day. We therefore used a freshly prepared solution for each day's experiments, except on rare occasions.

Results.—The results presented in table 1 indicate that animals were not easily sensitized by exposure for one-quarter to one-half hour. One of 11 animals showed signs of mild anaphylaxis after an intravenous test injection.

TABLE 1.—*Summary of Experiments on All Animals*

Animal No.	Sensitizing Dose Length of Exposure in Inhalation Chamber, Hr.	Result*	Animal No.	Sensitizing Dose Length of Exposure in Inhalation Chamber, Hr.	Result*	Animal No.	Sensitizing Dose Length of Exposure in Inhalation Chamber, Hr.	Result*
1	¼-½	Negative	12	1-3	Negative	40	4-5	Death
2		Negative	13		Death	41		Death
3		Negative	14		Negative	42		+
4		Negative	15		++	43		+++
5		Negative	16		Negative	44		Death
6		Negative	17		Death	45		Death
7		+	18		Death	46		Death
8		Negative	19		Negative	47		Death
9		Negative	20		Death	48		Negative
10		Negative	21		Death	49		Death
11		Negative	22		Death	50		Death
			23		++	51		Death
			24		Negative	52		Death
			25		Negative	53		Death
			26		Death	54		Death
			27		Negative	55		Negative
			28		Death	56		Death
			29		Negative	57		Death
			30		Negative			
			31		Death			
			32		Negative			
			33		Negative			
			34		Negative			
			35		Death			
			36		Negative			
			37		Death			
			38		Negative			
			39		Negative			

* In this table, "+" indicates signs suggestive of anaphylaxis; "++," marked dyspnea, scratching and convulsions; "+++," severe dyspnea, convulsions and collapse; "death," lethal anaphylaxis. The shock dose was a primary intravenous injection of 0.5 cc. dander extract.

Less than 50 per cent of the animals which inhaled the dander for one to three hours were sensitized.

Those sensitized were profoundly affected and died in anaphylactic shock when given the intravenous injection.

Of 18 animals exposed for four to five hours, the overwhelming majority were profoundly sensitized.

Since the animals exposed in the dust chamber were of approximately the same age and weight and since they were all procured from

7. Longcope, W. T.; O'Brien, D. P., and Perlzweig, W. A.: Antigenic Properties of Extracts of Horse Dander, J. Immunol. **10**:599, 1925.

the same source, it appears that the length of exposure was the factor which chiefly influenced the difference in results. The animals exposed for a longer period were sensitized in greater number than the animals which had a shorter contact with the antigenic dust. The optimum period for regular sensitization seems to be one hour a day for five days.

OBSERVATIONS ON REPEATED SHOCK CONTACTS WITH ANTIGENIC DUST ADMINISTERED TO ANIMALS SENSITIZED EXCLUSIVELY THROUGH INHALATION

In these experiments normal animals were repeatedly exposed to the specific dust both for sensitization and for shock. The length of contact

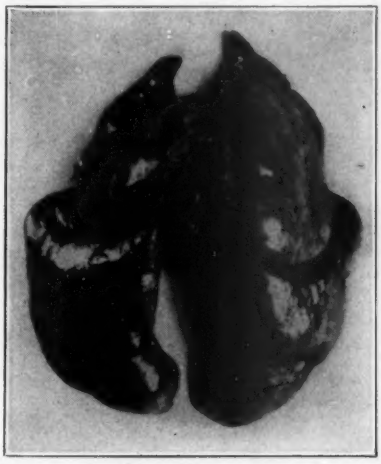

Fig. 2.—Lung removed from a sensitized animal which died three minutes after shock contact with dry horse dander in the inhalation chamber.

and the intervals between exposures were varied with the different groups, as will be described. The experiments are summarized in tables 2 through 7.

In an earlier paper[1] we presented instances of several animals sensitized by inhalation which actually died in anaphylaxis from the subsequent inhalation of dry antigen; the lungs were typical of lethal anaphylaxis (fig. 2).

All the animals in the group were finally given injections of dander extract to determine (1) whether the symptoms manifested in the dust chamber were those of hypersensitiveness and (2) whether the animals which did not react in the chamber were sensitized. The symptoms noted after injection are listed in table 1.

TABLE 2.—*Summary of Experiments on Group A* *

Day of Experimental Period	Time of Exposure	Degree of Asthma									
		Animal 847	Animal 861	Animal 850	Animal 859	Animal 862	Animal 853	Animal 852	Animal 849	Animal 854	Animal 857
Inhalation											
1 to 12..... (1½ mo. normal environment)	15 min. daily	0	0	0	0	0	0	0	0	0	0
58.....	5 min.	+	0	0	0	0	0	0	0	0	0
59.....	5 min.	+	0	0	0	+	0	0	+	0	0
60.....	5 min.	+	+	+	+	0	0	0	0	0	0
61.....	5 min.	0	+	0	0	0	0	+	0	0	0
62.....	5 min.	+	+	+	+	0	0	0	0	0	0
63..... (1 mo. normal environment)	5 min.	+	++	+	0	0	0	0	0	0	0
94..... (2 wk. normal environment)	5 min.	+++	+++	+++	+++	+++	+++	0	+	0	0
Intravenous injection of 0.2 cc. dander extract											
109.....		Death	Death	Death	Death	Death	Death	+++	+	0	0

* In tables 2 to 7, inclusive, "+" indicates signs suggesting asthma (moderate dyspnea, scratching, irritability, moderate roughing of fur); "++," mild asthma (definite dyspnea and air hunger, scratching, roughing of fur, occasional suffusion of eyes) and "+++," severe asthma (severe pounding dyspnea, dilated nares, extreme air hunger, often resulting in convulsive movements or collapse, pronounced roughing of fur, final recovery).

SUMMARY OF EXPERIMENTS

Group A.—In this experiment animals were exposed fifteen minutes daily for twelve days. After the initial stage, they were again repeatedly exposed for periods and at intervals indicated in table 2, with results as noted.

This experiment suggests that when animals are subjected to short contact (fifteen minutes) with an antigenic dust many exposures are necessary before sensitization is definitely established. On the other hand, it may indicate that after a comparatively brief initial sensitizing stage animals are only mildly sensitized and that shock exposures for as short a time as five minutes do not evoke reactions with any regularity. Some animals had suggestive symptoms; but animal 852, for example, had no symptoms from inhalation, although it was sensitized, as is evidenced by the profound anaphylaxis which resulted from the test injection.

TABLE 3.—*Summary of Experiments on Group B* *

Day of Experimental Period	Time of Exposure	Degree of Asthma					
		Animal 970	Animal 976	Animal 977	Animal 986	Animal 978	Animal 985
Inhalation							
1 to 12 (3 wk. normal environment)	30 min. daily	0	0	0	0	0	0
34	10 min.	++	+	0	0	0	0
35	10 min.	++	+	+	+	0	0
36	10 min.	+	++	+	+	0	0
37 (2 wk. normal environment)	10 min.	+++	+++	+++	+++	+++	+++
Intravenous injection 0.5 cc. dander extract							
52		Death	Death	Death	+++	Death	+++

* See footnote to table 2.

When the twelve sensitizing exposures of fifteen minutes each were fortified by six additional five minute exposures, animals 847, 850, 853, 859, 861 and 862 appeared to become more highly sensitive. They manifested severe asthmatic symptoms when they were again exposed to the dust, ninety-four days after the initiation of the experiment. Intravenous injection clearly shows that the inhalation reactions were those of specific hypersensitiveness. These animals gave no evidence of desensitization.

It must be noted that certain animals (854 and 857) were resistant throughout the experiment.

Group B.—Sensitizing exposures were increased to half an hour daily for twelve days. The subsequent periods and intervals, together with results, are given in table 3.

With an increase in the length of initial exposures there seems to be a definite speeding up of sensitization, and the animals react more readily after a shorter time. Severe asthmatic symptoms did not appear

in the animals of group A until the ninety-fourth day, as compared with the thirty-seventh day in group B.

It will be noted that reactions occurred on repeated daily exposures without the appearance of antianaphylaxis, which is usually observed after repeated daily parenteral injections.

TABLE 4.—*Summary of Experiments on Group C* *

Day of Experimental Period	Time of Exposure	Degree of Asthma				
		Animal 735	Animal 737	Animal 753	Animal 755	Animal 757
Inhalation						
1 to 7 (2 wk. normal environment)	1 hr. daily	0	0	0	0	0
22	15 min.	+++	++	0	0	0
23	15 min.	0	0	0	+	+
24	15 min.	+	0	0	0	0
25	15 min.	0	0	0	0	0
26	15 min.	++	++	+	+	0
27	15 min.	+++	+	++	+	+
28 (1 wk. normal environment)	15 min.	+++	+++	+	++	++
Intravenous injection 0.5 cc. dander extract						
36		+++	Death	Death	+++	Death

* See footnote to table 2.

TABLE 5.—*Summary of Experiments on Group D* *

Day of Experimental Period	Time of Exposure	Degree of Asthma							
		Animal 530	Animal 531	Animal 534	Animal 538	Animal 537	Animal 533	Animal 536	Animal 532
Inhalation									
1 to 12 (4 wk. normal environment)	2 hr. daily	0	0	0	0	0	0	0	0
41 (2 wk. normal environment)	10 min.	0	0	0	0	0	++	++	0
56	5 min.	+	++	+	+	+	++	0	0
57	20 min.	+	++	++	++	+++	0	0	0
58	15 min.	+	+	++	++	++	+	0	+
59 (2 wk. normal environment)	1 hr.	++	++	++	+++	++	+	0	0
Intravenous injection 0.5 cc. dander extract									
74		Death	Death	Death	Death	+++	++	Death	++

* See footnote to table 2.

Group C.—The sensitizing exposures were lengthened still further, to one hour each day for seven successive days. The subsequent periods and intervals and the results in the animals thus exposed are noted in table 4.

With further increase in the length of the initial exposures sensitization is even more rapidly and more regularly established.

The absence of antianaphylaxis must again be remarked.

Group D.—Animals were exposed two hours each day for twelve days. The results are presented in table 5.

These animals, which were exposed for a total of twenty-four hours, did not have asthmatic symptoms any earlier than animals in group C, which had been sensitized for a total of seven hours. We may conclude, therefore, that five to seven hours of exposure to an antigenic dust is the optimum sensitizing period.

Another point of interest in this particular experiment is the fact that we varied the length of the shock exposure from five minutes to one hour.

Again it is noted that certain animals manifest symptoms each time they are exposed to inhalation of dust (absence of antianaphylaxis), while others react irregularly and yet others not at all.

Group E.—This group of animals was exposed one hour daily for seven successive days. The interval between subsequent exposures was kept constant at two weeks (table 6).

The striking feature presented by this group, which had an optimum period for sensitization and were subsequently exposed at regular two week intervals, is the great regularity with which asthmatic symptoms appeared. It is possible that the optimum conditions for sensitization and shock may in a measure account for the uniformity of reaction.

Group F.—In the last experiment of this series 4 animals were exposed for one-half hour intervals practically every day for forty-eight days (table 7).

In this experiment an attempt was made to determine what reactions would ensue if animals were exposed almost daily for a long period. It is noted that as early as the thirteenth day after the first exposure animals begin to manifest asthmatic symptoms. It is possible that sensitivity may appear even earlier, but it is difficult to conceive that sensitization can be established sooner than the ninth or tenth day, when the antibodies which are formed early are known to make their first appearance.

Once more it is demonstrated that antianaphylaxis, or refractoriness, does not occur regularly, as it does after repeated parenteral injections. Animal 1356 presented a striking instance of apparent resistance to sensitization through inhalation: This animal had only eight attacks of mild respiratory distress, even though it was exposed forty-three times, and it reacted negatively to the intravenous test injection. Animal 1349, which showed profound asthma after the majority of exposures, on several occasions had no symptoms. It is interesting that on the last three exposures it manifested decreasing reactivity and that when given the intravenous test injection it was absolutely refractory. In this particular instance repeated profound reactions may actually have resulted in antianaphylaxis.

TABLE 6.—*Summary of Experiments on Group E* *

Day of Experimental Period	Time of Exposure	Degree of Asthma							
		Animal 1027	Animal 1148	Animal 1293	Animal 1296	Animal 1298	Animal 1300	Animal 1234	Animal 1235
Inhalation									
1 to 7	1 hr. daily	0	0	0	0	0	0	0	0
(2 wk. normal environment)									
22	5 min.	+++	++	++	+++	++	+	+++	+++
(2 wk. normal environment)									
37	30 min.	++	+++	+++	++	++	+++	+++	+++
(2 wk. normal environment)									
52	10 min.	+++	++	++	+++	+++	+	++	+++
(2 wk. normal environment)									
67	15 min.	+++	++	++	+++	++	++	++	++
(2 wk. normal environment)									
82	15 min.	++	+++	+++	++	+++	+++	++	++
(2 wk. normal environment)									
97	15 min.	+++	++	++	+++	++	+++	++	++
(2 wk. normal environment)									
112	15 min.	+++	++	++	++	++	+++	++	++
(1 wk. normal environment)									
Intravenous injection 0.5 cc. dander extract									
120		Death	Death	+++	Death	Death	Death	+++	Death

* See footnote to table 2.

RESPONSE OF VARIOUS SMOOTH MUSCLE ORGANS IN ANIMALS SENSITIZED THROUGH INHALATION

Although bronchial asthma in the human subject is as a rule limited to the pulmonary structure, there are often associated allergic manifestation in other organs. The demonstration of the positive allergic

TABLE 7.—*Summary of Experiments on Group F* **

Day of Experimental Period	Degree of Asthma			
	Animal 1355	Animal 1357	Animal 1349	Animal 1356
Inhalation				
1 to 12	0	0	0	0
13	+	+	0	0
14	+++	0	++	0
15	0	0	0	0
16	++	++	++	+
19	++	++	0	0
20	+++	+++	++	0
21	++	+++	++	0
23	0	+++	+++	+
24	+	++	++	+
26	++	+++	++	+
27	++	+++	++	0
28	+	+++	++	0
29	+	++	++	0
30	+	+++	++	0
33	+	+++	++	0
34	+++	++	0	0
35	+++	+++	0	+
36	++	+++	0	+
39	+++	+++	+++	0
40	+++	+++	+++	+
41	+++	+++	+++	0
43	+++	+++	+++	0
46	++	++	++	0
48	+++	+++	+++	+
(1 wk. normal environment)				
53	++	+++	+++	0
55	++	++	++	0
57	+	+	0	0
60	++	++	++	0
62	++	++	+++	0
(2 wk. normal environment)				
77	+++	++	++	0
(2 wk. normal environment)				
93	+++	+++	+	0
(2½ mo. normal environment)				
Intravenous injection 0.5 cc. dander extract				
154	Death	Death	0	0

* See footnote to table 2. The time of exposure was thirty minutes daily.

cutaneous reaction and the presence of passive sensitization antibodies (Prausnitz-Küstner) in the blood stream of asthmatic patients give added evidence of the general nature of the sensitization.

The question is raised whether in the guinea pig sensitization from inhalation is limited to the respiratory tract or other organs are also involved. In a previous paper [2] we showed that offspring of mothers sensitized to inhaled dry horse dander were either actively or passively sensitized in utero. When these offspring were brought into contact

with the dust for the first time, without previous injection or exposure, those that were sensitized in utero manifested asthmatic symptoms. As the sensitization of the fetus results from the passage of either antigen or antibody from the maternal to the fetal circulation, this could be taken as evidence that inhaled antigen enters the blood stream. There were, however, instances of mothers who were sensitized and who manifested asthmatic reactions when they came in contact with antigenic dust but whose offspring showed no such symptoms on contact with dust. Is it possible that in such mothers the pulmonary structures alone were sensitized?

Methods.—Several methods were considered for the study of this question. The establishment of positive cutaneous reactions as a result of sensitivity induced through inhalation would indicate general sensitization. The well known difficulties inherent in the demonstration of cutaneous reactions in the guinea pig would make pursuit in this direction unfruitful. The presence of antigen in the blood stream resulting from inhalation would indicate absorption but not necessarily general sensitization. The determination of specifically related antibodies in the blood presented technical objections. These three approaches to the problem were therefore abandoned in favor of the following method:

Virgin guinea pigs, weighing between 200 and 350 Gm., were used.

Procedure with Dry Antigen: Guinea pigs were exposed to horse dander dust one hour a day for five consecutive days. Three weeks later the animals were treated as follows: Step 1. Laparotomy was performed with the animal under ether anesthesia, and a uterine horn was removed for the determination of sensitization to horse dander extract by the Schultz-Dale method. The laparotomy incision was then closed.

Step 2. One hour after recovery from anesthesia the animal was given an intravenous injection of horse dander extract.

Procedure with Liquid Antigen: Animals received a total of 17 drops of horse serum in each nostril, by medicine dropper, over several days. The animals were held in an inverted position, according to the method suggested by Petragnani,[8] in order that seepage of the antigen into the trachea might be avoided. Three weeks later steps 1 and 2, just described, were carried out with use of horse serum instead of dander extract for the test injection.

SUMMARY OF EXPERIMENTS WITH DRY DANDER

A total of 37 animals were utilized in this experiment.

Group A.—There were 18 animals, 16 of which manifested lethal anaphylaxis after intravenous injection; 2 animals showed marked anaphylaxis with recovery. In no instance was the strip of the uterus of any value in determining whether this remote organ was sensitized. Either inertia or hyperactivity made interpretation of the reaction impossible.

The animals in this series were unquestionably sensitized, as they showed immediate anaphylactic reactions after intravenous injection. The indeterminateness of the uterine reaction, however, still leaves the question open as to whether an organ other than the lung is sensitized.

8. Petragnani, G.: Anafilassi a deanafilassi per la via nasale, Policlinico (sez. med.) **29**:446, 1922.

Group B.—Seven animals failed to react on intravenous injection and gave negative uterine reactions, from which it may be concluded that they were not sensitized by repeated exposure to horse dander dust.

Group C.—Of 6 animals given an intravenous test injection, 5 died in anaphylactic shock and 1 showed marked symptoms with recovery. The uterine strips from these animals reacted negatively on contact with dander extract, but all responded to the normal uterine constrictor, histamine phosphate. This is illustrated in figure 3.

The indications are that in this group of animals the bronchiolar musculature was sensitized but the uterus was not.

Group D.—In this group, consisting of 6 animals, all of the uterine strips gave positive Schultz-Dale reactions, an example of which is shown in figure 4. All of the animals also responded with typical anaphylactic shock after intravenous injection.

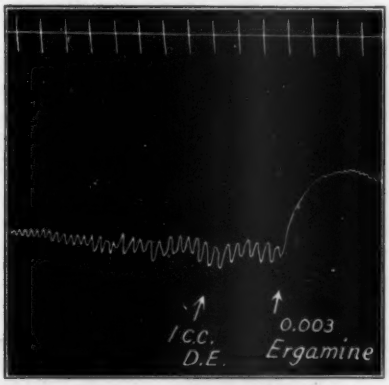

Fig. 3.—Animal 1459 (240 Gm.) was nasally sensitized with dry horse dander for five hours from May 21 to May 26, 1928. On June 26 it was etherized, and the uterine horn was removed for the Dale experiment. When 1 cc. of dander extract was added to the bath the muscle did not respond. This was shown to be a truly negative reaction, for the muscle responded typically to the addition of histamine. When the animal had recovered from the anesthesia it was given an intravenous injection of 0.5 cc. of dander extract, and it died in typical anaphylactic shock. This indicates local pulmonary sensitization.

From this series of experiments it appears that antigens which have been inhaled in a dry state may enter the blood stream and sensitize a remote organ as well as the lungs.

SUMMARY OF EXPERIMENTS WITH HORSE SERUM

A total of 12 animals were given nasal instillations.

Group A 1.—In 3 animals the reaction of uterine strip could not be interpreted because of inertia or overactivity. The animals, however, reacted positively to intravenous injection.

Group B 1.—Four animals gave entirely negative reactions.

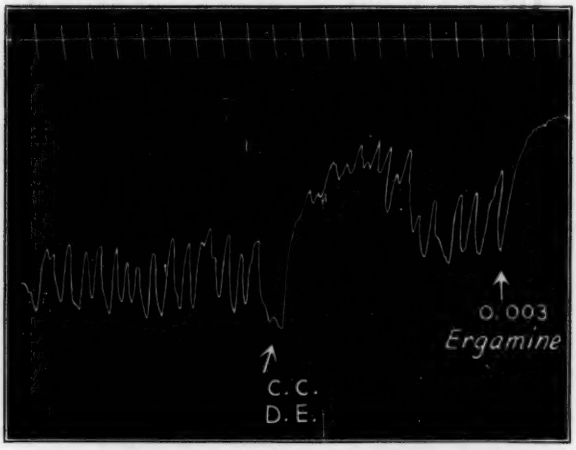

Fig. 4.—Animal 1551 (215 Gm.) was nasally sensitized with dry horse dander for five hours from July 16 to July 21, 1928. On August 14 the animal was etherized, and the uterine horn was removed for the Dale experiment. On addition of 1 cc. of dander extract to the bath the muscle responded with a definite contraction, which indicated that there was generalized sensitization. After relaxation, the addition of histamine caused a contraction of the same intensity. When the animal recovered from the anesthesia it was given an intravenous injection of 0.5 cc. of dander extract, and it died in typical anaphylaxis.

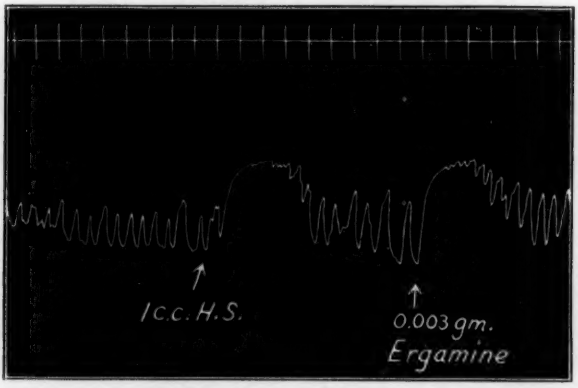

Fig. 5.—Animal 1305 (240 Gm.) was sensitized nasally from Jan. 16 to Jan. 28. 1928, with a total of 17 drops of horse serum in each nostril. On February 14 the animal was etherized, and the uterine horn was removed for the Dale experiment. After recovery from the anesthesia 0.5 cc. of horse serum was injected intravenously. Death from typical anaphylactic shock followed the injection. The uterus responded on addition of 1 cc. of horse serum to the bath. This response was maximal, as it was identical with that elicited after the addition of histamine to the bath. General sensitization is indicated.

Group D 1.—Five animals all responded positively to both the Schultz-Dale (fig. 5) and the intravenous test.

In no case was the reaction of the uterine strip negative and the reaction to the intravenous test positive, as with group C of the animals sensitized by inhalation of dry dander.

When a dry antigen inhaled in a natural manner is used as the sensitizing agent, the respiratory tract alone is affected in certain animals, while in other animals similarly sensitized both the pulmonary structure and the uterus are affected.

A different result ensues when the sensitizing substance is a liquid antigen which is instilled into the nares. None of the animals in our series treated with liquid antigen evidenced bronchiolar sensitization without uterine sensitization. We should have liked to carry this experiment further, making the series of tests with the liquid antigens more comparable numerically with those involving the dry antigen. The experiments, however, were too laborious to be carried further at the time. We must therefore regard the absence of single organ sensitivity resulting from inhaled liquid antigens as highly suggestive rather than conclusive.

After this work was completed, we came on the study of Kallos and Pagel [9] in which they reported that uteri removed from allergic animals which died from the inhalation of sprayed liquid antigen all responded to the specific antigen.

COMMENT ON EXPERIMENTAL RESULTS

Previous failures with the inhalation experiment may in part be attributed to the inadequacy of exposure to the antigen. Petragnani [8] described instances of sensitization which resulted from a single nasal instillation. The present study, however, indicates that exposures of at least one hour for five successive days are essential before sensitization is established in the majority of animals. When the daily contacts were of short duration many more exposures were necessary.

One cannot conclude that the quantitative factor alone determines whether sensitization will be established. In spite of the fact that animals of approximately the same weight and age received similar exposures, they were not sensitized to the same degree, and some animals were not sensitized at all.

It has been assumed that sensitization is established in the experimental animal with regularity, whereas in man the disposition to become sensitized depends on genetic factors. These studies make it evident that certain animals are highly susceptible and become sensitized after short contacts, while others remain resistant although exposed repeatedly. When a situation produced in the animal is similar to that which occurs

9. Kallos, P., and Pagel, W.: Experimentelle Untersuchungen über Asthma bronchale, Acta med. Scandinav. **91**:292, 1937.

naturally in the human subject, individual differences in susceptibility become more apparent. The host factor in relation to hypersensitiveness in animals has been commented on by Lewis and Loomis,[10] Manteufel and Preuner [11] and Zinsser and Enders.[12]

Apparently, the concept to be derived from the experiments reported in this study is that animals as well as human beings vary greatly in their capacity to become sensitized.

Although important innate differences in susceptibility and resistance exist both in human beings and in animals, we do not think they are decisive. Our experiments suggest that adequate exposures [13] to an allergenic dust may overcome the intrinsic resistance of most animals.

In the course of this report we have repeatedly called attention to the fact that sensitized animals subjected to repeated exposure to dust do not as a rule manifest the so-called antianaphylactic state, which is observed in animals after repeated parenteral injection. This observation was also made by Busson,[14] Petragnani,[8] Sewall,[15] and Kallos and Pagel.[9] Ulrich [16] similarly found that repeated inhalations of dry pollen on alternate days induced not antianaphylaxis but a steady rise of susceptibility.

This general absence of antianaphylaxis, particularly in animals in which as many as twenty-eight successive attacks were induced by daily contacts with the specific dust, is closely analogous to that which occurs in the asthmatic human being. Cannot this be likened to human status asthmaticus? Yet, as we have pointed out, absence of antianaphylaxis was constantly observed in our animals. Like the asthmatic human being

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10. Lewis, P. A., and Loomis, D.: Allergic Irritability: II. Anaphylaxis in the Guinea Pig as Affected by the Inheritance, J. Exper. Med. **41**:327, 1925.

11. Manteufel, P., and Preuner, R.: Experimentelle Untersuchungen über den anaphylaktischen Schock als Modellversuch für allergische Krankheiten, Ztschr. f. Immunitätsforsch. u. exper. Therap. **80**:65, 1933.

12. Zinsser, H., and Enders, J. F.: Variation in the Susceptibility of Guinea Pigs to Reversed Passive Anaphylaxis, J. Immunol. **30**:327, 1936.

13. In this connection it is interesting to note the behavior of guinea pigs in the dust chamber. They have a tendency to huddle together in a corner, burying their noses in each other's fur or pressing them against the wall. Thus one is led to suspect that some animals inhale more of the antigen than others, even though to all intents and purposes they are exposed to the same environment. Busson and Ogata (Busson, B.: Ueber Eiweiss Anaphylaxie von den Luftwegen aus, Wien. klin. Wchnschr. **24**:1492, 1911. Busson, B., and Ogata, N.: Gibt es Beziehungen zwischen den menschlichen Idiosynkrasien und der tierexperimentellen Anaphylaxie? ibid. **37**:820, 1924. Busson, B.: Zur Frage der menschlichen Idiosynkrasie und der tierexperimentellen Anaphylaxie, ibid. **38**:219, 1925) made similar observations.

14. Busson, 1911, cited in footnote 13.

15. Sewall, H.: Experimental Asthma in the Guinea Pig, J. Lab. & Clin. Med. **11**:3, 1917.

16. Ulrich, H. L.: Experimental Pollinosis, J. Immunol. **3**:453, 1918.

who has periods of remission in spite of contact with an offending allergen, our experimental animal had temporary periods of non-reactivity.

It is possible that neutralization of antigen by circulating antibodies occurs after parenteral injection but that inhalation of specific dust brings the antigen into direct contact with the sensitized tissues without the intervention of humoral antibodies. This may also explain why Seegal and Seegal [17] were unable to demonstrate desensitization in the locally sensitized eye.

Clinically there may be local allergic symptoms limited to the eye or nose with absence of cutaneous reactions, particularly in allergic children. Peshkin [18] has shown that dry pollen applied directly to the eye will result in a local allergic response in hay fever sufferers with negative cutaneous reactions. I have followed such cases and observed the gradual development of positive cutaneous reactions. Stevens [19] and Ramirez [20] reported cases of asthma and of hay fever, respectively, in which dermal reactions were not evidenced yet an immediate allergic response developed from inhalation of a specific allergenic dust. Ulrich,[16] who sensitized guinea pigs with dry pollen insufflated into the nostrils, found that repeated contacts almost always resulted in local nasal reactions resembling hay fever but only occasionally were true asthmatic symptoms obtained. Furthermore, results of precipitin tests on the blood were negative, and intracardial injection of pollen extract produced no symptoms. Cooke, Flood and Coca's [21] definition of hay fever as a clinical symptomatic expression of local hypersensitiveness may therefore be correct only in those cases in which reactions to cutaneous tests are negative and Prausnitz-Küstner antibodies are absent.

We found that when liquid antigens were inhaled both lung and uterus were sensitized. On the other hand, when a dry antigen was

17. Seegal, D., and Seegal, B. C.: Local Organ Hypersensitiveness: III. Further Observations on Its Experimental Production in the Rabbit Eye, J. Exper. Med. **54**:249, 1931.

18. Peshkin, M. M.: A Dry Pollen Ophthalmic Test in Pollen Asthma and Hay Fever Patients Negative to Cutaneous Tests, J. Allergy **3**:20, 1931.

19. Stevens, F. A.: A Comparison of Pulmonary and Dermal Sensitivity to Inhaled Substances, J. Allergy **5**:285, 1934.

20. Ramirez, M. A.: Relation of Allergy to the Diseases of the Respiratory Tract, in Graduate Fortnight of the New York Academy of Medicine, Philadelphia, W. B. Saunders Company, 1936.

21. Cooke, R. A.; Flood, E. P., and Coca, A. F.: Hay Fever: Nature of the Process and of the Mechanism of the Alleviating Effect of Specific Treatment, J. Immunol. **2**:217, 1917.

the sensitizing substance, certain of the animals had respiratory symptoms with no uterine reactivity, while other animals evidenced both pulmonary and uterine sensitization.[22]

It seems reasonable to assume, therefore, that in the animal, just as in man, sensitization induced through the inhalation of a dry antigen may be limited to a single organ. Conceivably sensitization is at first limited to the organ that comes in direct and immediate contact with the antigen. Continued exposure may bring about heightened sensitivity, and other organs may become involved. The differentiation between regional and general sensitivity may, therefore, depend in a measure on temporal and quantitative factors.

II. THEORETIC CONSIDERATIONS

FACTORS INFLUENCING RESPIRATORY SENSITIZATION AND SHOCK

Anaphylaxis induced through inhalation, as we have shown, differs from the parenterally induced form in several respects. The differences are largely due, we believe, to the character of the antigen used, the manner of presentation of the antigen to the host and the locus of contact with and absorption of the material.

Studies with Liquid Antigens.—Is the Material Absorbed by the Nasopharynx? Petragnani [8] instilled antigen intranasally in the guinea pig, holding the head in an inverted position. He also produced shock intranasally in tracheotomized animals. During such injections in tracheotomized pigs he never saw the serum issue from the upper, cut section of the trachea, no matter with what force the antigen was injected. The excess passed into the buccal cavity or the esophagus. (This, however, does not seem to rule out seepage through the intact trachea during inspiration.) He concluded that the material was absorbed solely by the olfactory cells and the olfactory pharyngeal mucosa.

Blumgart [23] found with cats that crystalloids and colloids traverse the nasopharynx and are absorbed by way of the olfactory nerve cells to the systemic lymphatics.

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22. With our method, it must be remembered, the uterus of an animal sensitized by inhalation was removed with the subject under anesthesia before the intravenous shock injection was given, so that the question of the desensitization of the uterus, raised by H. L. Alexander, W. G. Becke and J. A. Holmes (Reactions of Sensitized Guinea Pigs to Inhaled Antigens, J. Immunol. **11**:175, 1926), is ruled out. In their experiments, the uteri were removed after anaphylactic shock was induced through inhalation, but the animals were sensitized by intraperitoneal injection.

23. Blumgart, H. L.: A Study of the Mechanism of Absorption of Substances from the Nasopharynx, Arch. Int. Med. **33**:415 (April) 1924.

Does Absorption Take Place Through the Trachea? Jones' studies [24] refuted the conclusion of Ishioka [25] and Besredka [26] that the trachea serves as an organ of absorption. He clearly showed that the intact trachea is signally impermeable to the passage of colloid material and that the alveoli serve as the absorbing membrane. Absorption through the lung, however, is extremely slow, taking several hours longer than absorption by the intraperitoneal route.

Does the Material Come in Direct Contact with the Bronchioles and Alveoli, and Is It Absorbed from This Portion of the Respiratory Tract? Sternberg [27] found that colloidal dyes (carmine and collargol [a preparation of colloidal silver and silver oxide]) were never found in the nasopharynx after swabbing but always seeped down to the alveoli. Small amounts, however, were absorbed locally by the nasopharynx, which he attributed to mucosal defects. With dogs, he showed further that nasal swabbings with argochrome (a silver compound of methylthionine chloride) result in a green color of the urine, which he attributed to absorption through the alveoli.

Busson [14] sprayed serum mixed with india ink and found particles in the lung parenchyma.

Alexander, Becke and Holmes,[28] however, have presented the most concrete evidence for the demonstration of serum in the alveoli. They removed and macerated the lungs of animals shocked by spraying, carefully separating the lungs from the trachea. This material provoked a positive reaction in a sensitized uterine horn.

Jones [24] also demonstrated serum in the macerated lungs of guinea pigs by means of the precipitin test. The serum was injected via the trachea.

Colin,[29] in 1873, described an experiment in which he introduced intratracheally into a tracheotomized horse a continuous stream of warm (30 to 35C.) water at a rate of 6 liters per hour for three and a half hours without causing any noticeable discomfort to the subject. When the animal was killed, at the end of the experiment, the observer could not detect any water in the trachea or bronchi; it had been thoroughly absorbed.

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24. Jones, F. S.: Permeability of the Lining of the Lower Respiratory Tract for Antibodies, J. Exper. Med. **40**:73, 1924; Effects of the Intratracheal Administration of Foreign Serum, ibid. **40**:63, 1924.

25. Ishioka, S.: Zur Histologie der anaphylaktischen Pneumonie, Deutsches Arch. f. klin. Med. **107**:500, 1912.

26. Besredka, A.: De l'action des serums par la voie respiratoire, Ann. Inst. Pasteur **34**:51, 1920.

27. Sternberg, H.: Beiträge zur Physiologie und Pathologie der Schleimhaut der ober Luftwegen: II., Ztschr. f. Hals-, Nasen- u. Ohrenh. **8**:275, 1924.

28. Alexander, Becke and Holmes, cited in footnote 22.

29. Colin, G.: Traité de physiologie comparée des animeaux, considée dans ses rapports avec les sciences naturelles, la médecine, la zootechnie et l'economie rurale, ed. 2, Paris, J. B. Baillière & fils, 1873, p. 109.

Does an Arthus-Like Phenomenon Occur in the Lung? Ströbel [30] noted that serum injected into the trachea did not cause general anaphylaxis, but on the day following the injection he found a typical pneumonic exudate, which he likened to the Arthus phenomenon.

Busson [14] also found that four days after sensitized animals were sprayed they showed hemorrhages and infarcts; like Friedberger, he stated the belief that it was due to pulmonary anaphylatoxin.

Opie [31] reproduced the phenomenon of Arthus in the lung of an immune animal. Injection of 0.2 cc. of horse serum through the thoracic wall into the lung of an immunized rabbit caused localized consolidation, with leukocytes and edema surrounding a central focus of necrosis. The same antigen injected into a normal animal was absorbed from the lung with no noteworthy change.

Fried [32] reported that rabbits sensitized by repeated intraperitoneal injections of horse serum contracted acute lobar pneumonia when the last injection was introduced into the lungs via the trachea.

Studies with Antigenic Dusts.—Friedberger and Kamio [33] were unable to sensitize or shock animals by the inhalation of dry horse or cattle dander. Van Leeuwen, Bien and Varekamp [34] failed likewise with dry pollen and dry horse serum. Wichelhausen [35] sprayed bean and pea meal into the nasal passages and conjunctiva, but no allergic reactions developed in the animals.

Reproduction of Hay Fever and Asthma in Animals with Inhalants Commonly Affecting Human Beings: Ulrich [16] was successful in reproducing the syndrome of hay fever by insufflating dry ragweed pollen into the nares of guinea pigs.

My co-workers and I successfully sensitized and shocked animals by the use of dry horse dander [1] and castor bean dust [3] circulating in a specially devised chamber.

Prausnitz [36] recently exposed guinea pigs for many months to dry cotton dust by a method similar to ours and produced chronic conditions

30. Ströbel, H.: Ueber die anaphylaktische Reaktion der Lunge, München. med. Wchnschr. **59**:1538, 1912.

31. Opie, L. E.: Inflammatory Reaction of the Immune Animal to Antigen (Arthus Phenomenon) and Its Relation to Antibodies, J. Immunol. **9**:231, 1924.

32. Fried, B. M.: Allergic Inflammation of the Lungs: Pathogenesis of Lobar Pneumonia, Arch. Path. **18**:865 (Dec.) 1934.

33. Friedberger, E., and Kamio, T.: Gelingt es, beim Meerschweinchen experimentelle Beziehungen zwischen Asthma und Anaphylaxie nachzuweisen? Ztschr. f. Immunitätsforsch. u. exper. Therap. **37**:379, 1923.

34. Van Leeuwen, W. S.; Bien, Z., and Varekamp, H.: Experimentelle allergische Krankheiten, Ztschr. f. Immunitätsforsch. u. exper. Therap. **40**:552, 1924.

35. Wichelhausen, cited by Manteufel and Preuner.[11]

36. Prausnitz, C.: Investigations on Respiratory Dust Disease in Operatives in the Cotton Industry, Medical Research Council, Special Report Series, no. 212, London, His Majesty's Stationery Office, 1936.

resembling "cotton operatives' asthma." He demonstrated the presence of cotton dust in the alveoli of the guinea pigs that had inhaled it in a natural manner.

Van Leeuwen, Bien and Varekamp [34] produced respiratory symptoms in guinea pigs and dogs with mite-infected oats through inhalation in a chamber. Though there was an allergic element, the condition was largely infectious. These authors attributed the sensitivity manifested on first exposure in part to the toxicity of the material but expressed the belief that it was more likely that the animals were previously sensitized because of the ingestion or inhalation of infected grain or straw.

Locus of Absorption.—The trachea does not appear to be an organ of absorption, particularly in the light of Jones' [24] excellently formulated and controlled experiments. It appears from the evidence just presented that both the nasopharynx and the pulmonary structure may serve as absorbing and reacting areas, either with liquid or with dry antigens.

Manner of Presentation of the Material to the Host.—Besredka [26] and Renon and Mignot [37] used serum that was concentrated ten to twenty times (a syrupy concentrate consisting of 250 cc. of serum in which was dissolved 100 Gm. of dried serum). No shock ensued when this was injected into the larynx, nor, in Jones' experiments, did shock result from injection of serum into the intact trachea. The material was dissolved slowly and served to sensitize animals, but they were not easily shocked. In order to obtain uniform shock results, one must use finely sprayed material or finely powdered dusts. Great emphasis has been laid on this point by Busson,[14] Ströbel,[30] Alexander, Becke and Holmes [28] and, more recently, Manteufel and Preuner,[11] Prausnitz [36] and Kallos and Pagel.[9] The last-mentioned authors stated that the particles must be less than 0.005 mm. in diameter in order that the drops may penetrate into the alveoli of the lungs.

This may help to explain the failure of Friedberger and Kamio [33] and Van Leeuwen, Bien and Varekamp [34] to sensitize animals with horse and cattle dander, dry pollen and dry horse serum. Their material was too coarse. We succeeded because the horse dander dust and castor bean dust, defatted in preparation, was so fine that it passed through a 200 mesh sieve. Prausnitz,[36] who prepared cotton dust by a method similar to that first used by us, stated that ultramicroscopic examination of the dust floating in the air after the sample of cotton had been beaten revealed that there was practically no lower limit to the size of the dust particles.

The greater amount of the "fine dust fraction" actually consists of ultramicroscopic particles, i. e., of a size under 0.2 microns. It is clear that they will readily

37. Renon, L., and Mignot, R.: Sero-thérapie par la voie respiratoire, Compt. rend. Soc. de biol. **83**:209, 1920.

be inhaled into the finest and deepest portions of the respiratory system. They are even so fine as to be able, probably, to pass through the alveolar wall into the interalveolar tissue. Their relatively large surface will allow any of their constituents which are soluble in the alveolar mucus and in the intercellular lymph to enter into solution, as the case may be, in or beyond the alveolar surface.

EXPERIMENTAL STUDIES WITH INHALANTS IN THE HUMAN SUBJECT

The experimental work on respiratory anaphylaxis thus far presented was carried out primarily with guinea pigs. The question might therefore be raised as to whether the mechanism in the human subject is fundamentally the same as in the guinea pig. We shall examine, therefore, experimental work on the human subject.

Studies with Liquid Antigens.—Dzerzhgovski [38] and later Blumenau [39] actively immunized children to diphtheria toxin by the introduction of toxin-soaked tampons into the nares. More recently, Jensen [40] recommended the use of intranasal instillations of diphtheria toxoid rendered nontoxic by incubation with formaldehyde ("formol toxoid") as a complement to a single subcutaneous injection. By this procedure he definitely showed for human beings (and confirmed it for rabbits) that the titer of diphtheria antitoxin in the blood was definitely increased.

The work of Blumgart [23] similarly demonstrated that aqueous pituitary extract was absorbed through the nasal mucosa by the subject with diabetes insipidus and that this resulted in therapeutic improvement.

Work of a similar nature, but approached from a different point of view, was that of Simon and Rackemann.[41] Their aim was to show that hypersensitiveness can be established in human beings by absorption of antigens through the nasal mucous membrane. In this study, absorbent cotton was soaked in guinea pig serum and inserted into the nasal cavity. The 9 subjects were all suffering from inhalant allergy but were free of symptoms at the time. Applications of the serum were made at intervals varying from three days to two weeks or longer. Following the second and third applications, nasal symptoms developed in 4 cases. In 5 cases no nasal sensitization developed, yet in all 9 cases positive cutaneous reactions were obtained when the subjects were

38. Dzerzhgovski, S. K.: Active Immunization of Man to Diphtheria, Russk. vrach. **9**:753, 1910; abstracted, Ztschr. f. Immunitätsforsch. u. exper. Therap. **2**: 602, 1910.

39. Blumenau, N. R.: Active Antidiphtheritic Immunization of Children by Dzerzhgovski's Method, Russk. vrach. **10**:151, 1911; abstracted, Ztschr. f. Immunitätsforsch. u. exper. Therap. **3**:196, 1911.

40. Jensen, C.: Active Immunization Against Diphtheria by the Combined Subcutaneous and Intranasal Method, Proc. Roy. Soc. Med. **30**:1117, 1937.

41. Simon, F. A., and Rackemann, F. M.: Development of Hypersensitiveness in Man: II. Absorption of the Antigen Through the Nasal Mucous Membrane, J. Allergy **5**:451, 1934.

tested three weeks to two months later. There is not enough evidence to rule out primary toxicity of guinea pig serum, which was found to be a factor of significance by Ramsdell.[42] She found that the skins of normal human beings regularly show the immediate type of reaction to normal guinea pig serum in a dilution of 1:10 (used by Simon and Rackemann) and to a lesser degree to a dilution of 1:50. If the work of Simon and Rackemann is repeated with other substances, it will afford further proof that liquid antigens can be absorbed by the nasal mucosa, as is apparent from the reports of Dzerzhgovski, Blumenau, Blumgart and Jensen.

Of even greater interest is the unique experiment of Bonsfield and King-Brown.[43] They found difficulty in using the instillation method and used instead a finely atomized diphtheria toxoid made nontoxic with formaldehyde ("formol toxoid"). Adult volunteers were chosen. They

Antitoxin Content

Before Spraying, Units	14 Days After Second Spraying, Units
1/10	2
1/250	5
1/10	10
1/10	10
1/25	1/5
1/1,000	1/500
1/2	2 (1 spraying)

were put into a room 15 by 12 feet (4.57 by 3.66 meters) for fifty minutes. Into this chamber an atomizer ejected the vapor at the rate of 1 cc. per minute. The subjects frequently changed their position in order to receive equal exposures. They were exposed for two periods two weeks apart. Reactions following the first inhalation were negligible, but after the second they were rather severe in most cases, which was attributed to allergic sensitization. They consisted of headache, chills, fever, tightness of the chest and cough. The antitoxin content of the blood in each instance was considerably raised.

Studies with Dry Antigens.—It has been known for many years that industrial workers become sensitized to dry antigenic substances which they inhale. Among these may be cited veterinarians, grooms and cavalrymen, who become sensitized to animal dander; millers and bakers, to meal dust; apothecaries, to ipecacuanha; quinine factory

42. Ramsdell, S. G.: Reaction of the Human Skin to Normal and Immune Guinea Pig Serum, J. Immunol. **19**:217, 1930.

43. Bonsfield, G., and King-Brown, W. W.: Diphtheria Immunization with Finely Atomized Formol Toxoid, Lancet **1**:491, 1938.

workers, to quinine, and coiffeurs, wigmakers, dealers in skins and animal keepers, to hair. Ubiquitous substances, such as pollen and environmental dusts, give rise to symptoms in young as well as in older patients.

Recently several studies have appeared which emphasize factors of interest. For example, Colmes, Guild and Rackemann [44] studied a group of bakers and showed that about 40 per cent became cutaneously sensitive, although only 1 was clinically sensitive. This group worked in a scientifically controlled baking establishment, which may account for the infrequency of the clinical symptoms.

Salén and Juhlin-Dannfelt [45] tested a large number of persons belonging to different occupational groups. They found that on cutaneous test those exposed to occupational allergens reacted to the respective allergens more frequently than controls, who were of different occupational groups. These results indicated to the authors that a positive cutaneous reaction to allergens to which one is exposed, even though no symptoms are manifested, implies latent allergy.

Blumstein [46] reported on 19 patients skin-reactive to buckwheat, of whom only 8 were clinically sensitive. Most of the patients, however, reacted after inhalation but showed no symptoms on ingestion of buckwheat. The fact that they did not react on ingestion may be due to the change in allergenicity of the buckwheat due to cooking (Ratner and Gruehl [47]).

Cohen and his co-workers [48] presented the most exact experiments thus far made with respect to the nasal absorption of dry antigens by human beings. They used for these studies both normal and allergic subjects. The method employed was to sensitize passively a site on the arm with serum obtained from a patient allergic to ragweed. Twenty-four hours later dry pollen was insufflated into the nares, care being taken to have the patient avoid swallowing the material. The antigen was absorbed into the blood stream, as judged by the appearance of a wheal formation at the prepared site. This occurred in all of 50 normal subjects studied. The reaction appeared within fourteen to thirty-one

44. Colmes, A.; Guild, B. T., and Rackemann, F. M.: Studies in Sensitization: Influence of Occupation on Sensitization in Man as Determined in a Study of Thirty-Two Bakers, J. Allergy **6**:539, 1935.

45. Salén, E. B., and Juhlin-Dannfelt, C.: Ueber das Vorkommen von sogen. latenter Allergie, Acta med. Scandinav. **86**:505, 1935.

46. Blumstein, G. I.: Buckwheat Sensitivity, J. Allergy **7**:74, 1936.

47. Ratner, B., and Gruehl, H. L.: Anaphylactogenic Properties of Certain Cereal Foods and Breadstuffs: Allergenic Denaturation by Heat, Am. J. Dis. Child. **57**:739 (April) 1939.

48. Cohen, M. B.; Ecker, E. E.; Breitbart, J. R., and Rudolph, J. A.: The Rate of Absorption of Ragweed Pollen Material from the Nose, J. Immunol. **18**: 419, 1930.

minutes (average twenty-one and eight-tenths minutes). As reported in a subsequent paper, three of these authors [49] demonstrated by an ingenious method that intranasally absorbed antigen remains in the circulation for a period not exceeding twenty-four hours.

In persons with inhalant allergy, the time of absorption ranged from eighteen to sixty-nine minutes (average forty-one and nine-tenths minutes). This was demonstrated for 7 of 12 allergic patients. No reaction occurred in the remaining 5 patients during the period of observation, which varied from sixty-five minutes to two hours. When the pollen was insufflated in patients sensitive to ragweed a severe local nasal reaction occurred. No ragweed pollen could be demonstrated in the blood of such subjects after three hours of observation. The interesting point is that allergic subjects showed marked delay or even absence of absorption.

This work is of fundamental value in proving that a dry antigen can be absorbed by the nasopharynx of practically any normal person. The failure of absorption in specifically allergic subjects in whom a severe local reaction develops through direct contact with the allergen may be correlative to Opie's [50] work, which showed that inflamed tissues tend to retain injected antigen. The delayed absorption observed in allergic persons sensitive to substances other than pollen may be explained on the basis of diminished permeability due to the thickened basement membrane of the mucosa—an almost universal attribute of chronically allergic tissue, both nasal and pulmonary.

Leopold and Leopold [51] induced attacks in human asthmatic subjects with specific antigenic dust introduced into a dust-free chamber.

Probably the most fascinating group of studies were those made with silk. It was not generally known that silk contributes many air-borne particles in the modern household until the work of Figley and Parkhurst [52] appeared. They demonstrated conclusively that silk—or, more rightly, the gum or glue of the silkworm secretions present in the silk—exerts its effect in producing eczema as an inhalant rather than as a contactant.

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49. Cohen, M. B.; Ecker, E. E., and Rudolph, J. A.: The Disappearance Time of Circulating Ragweed Pollen Material After Absorption from the Nose and Throat, J. Allergy **1**:529, 1930.

50. Opie, E. L.: The Fate of Antigen (Protein) in an Animal Immunized Against It, J. Exper. Med. **34**:659, 1924.

51. Leopold, S. S., and Leopold, C. S.: Bronchial Asthma and Allied Allergic Disorders: Preliminary Report of Study Under Controlled Conditions of Environment, Temperature and Humidity, J. A. M. A. **84**:731 (March 7) 1925.

52. Figley, K. D., and Parkhurst, H. J.: Silk Sensitivity with Especial Reference to Its Role in Atopic Eczema, J. Allergy **5**:60, 1933.

Sulzberger and Vaughan,[53] utilizing the technic first employed by Cohen and his co-workers, confirmed the observations of Figley and Parkhurst. Dry silk powder sniffed into the nostril was absorbed directly into the blood stream. The absorption time was approximately that found by Cohen with pollen (twenty minutes). Thus Cohen's work on the absorption of dry antigens through the respiratory tract was corroborated, and the careful clinical observations and conclusions of Figley and Parkhurst were fortified.

Endemic Asthma: To Ancona [54] must go the credit for describing what may be called endemic asthma. Both Doerr [55] and Kallos and Kallos-Deffner [56] have pointed out that Grove's [57] criticism of Ancona's conclusions is unjustified.

An epidemic of this condition occurred among millers in a small village in Italy. They manifested symptoms of asthma associated with urticaria and dermatitis, which Ancona traced to sensitization from wheat which was infected with Pediculoides ventricosus. The outstanding feature was that only those who sifted and ground the infected wheat for long periods became sensitive. No particular family disposition was found. Unrelated persons who worked in the granary became affected, whereas their relatives who remained at home or worked at some other occupation were unaffected. The attacks occurred shortly after or during the shoveling, sifting or grinding of the damaged grain. Ancona experimentally produced the hemoclastic and asthmatic crisis by having the sensitive persons inhale the dust of the damaged grain, with which he also obtained positive cutaneous and intradermal reactions. The dust of the sound grain was innocuous.

Van Leeuwen, Bien and Varekamp [34] subsequently studied another form of endemic asthma in the lowlands of Holland. They attributed it to mite-infected oat grains. Because Cooke, Flood and Coca,[21] Friedberger and Kamio [33] and they themselves were unable to sensitize animals to pollen, dry dander and dry horse serum, respectively, by inhalation, Van Leeuwen and his co-workers stated the belief that the

53. Sulzberger, M. B., and Vaughan, W. T.: Experiments in Silk Hypersensitivity and the Inhalation of Allergen in Atopic Dermatitis, J. Allergy **5**:554, 1934.

54. Ancona, G.: Asma epidemico da "Pediculoides ventricosus," Policlinico (sez. med.) **30**:45, 1923.

55. Doerr, R.: Allergie und Anaphylaxie, in Kolle, W.; Kraus, R., and Uhlenhuth, P.: Handbuch der pathogenen Mikroorganismen, ed. 3, Jena, Gustav Fischer, 1929, vol. 1, pt. 2.

56. Kallos, P., and Kallos-Deffner, L.: Die experimentellen Grundlagen der Erkennung und Behandlung der allergischen Krankheiten, Ergebn. d. Hyg., Bakt., Immunitätsforsch. u. exper. Therap. **19**:178, 1937.

57. Grove, E. F.: Studies on Specific Hypersensitiveness: XXVI. On Asthma and Dermatitis Due to Hypersensitiveness to Pediculoides Ventricosus, J. Immunol. **12**:263, 1926.

assumption that true asthmogenic substances alone are the cause of asthma is unwarranted. Stimulated by the work of Ancona, they suggested that the strong primary action of the contaminating mite so irritated the membranes of the respiratory tract that the true allergen could then sensitize the tissues. They called this activating substance a miasmen. In sensitive persons who were exposed to the inhalation of the contaminated grain when they were free from symptoms there developed typical allergic symptoms and urticaria. Reactions to cutaneous tests with a watery extract of the pure oats were negative. Tests with an extract of the mites gave positive reactions, as well as tests with the oat residue freed from mites. The authors concluded that the reactions were due to the metabolic products of the mites in the oats. Cases have been cited of children suffering from allergy who slept near bins containing the infected grain and of farmers and merchants handling grains, flower bulbs and straw. Van Leeuwen and his associates compared this type of miasmen with paraphenylenediamine, a factor in tanner's asthma, and to emetine, in sensitivity to ipecacuanha. He went so far as to assert that sensitivity to bread and other meal-containing foods may be due to contaminated grain and that horse dander sensitivity may be due to mite-infected straw in the stable which gets into horses' hair.

The next example of endemic asthma, reported by Figley and Elrod,[58] occurred in the vicinity of a castor oil factory. Persons who worked in the factory or were within a mile of it were sensitized to the castor bean dust ejected from the chimneys. A large group of children in a school opposite the factory were affected. Housewives and children had their attacks at any time during the day or night. Sensitized persons living in this vicinity but working elsewhere had their attacks only at night, on returning to their homes. These authors proved their thesis by obtaining positive cutaneous reactions to castor bean.

Actuated by these observations, we (Ratner and Gruehl [3]) obtained castor bean dust (pomace) from the same factory for experimental purposes. Here too a primary toxic substance is present, namely, ricin. Animals died within forty-eight to seventy-two hours from typical ricin poisoning involving the adrenals and intestines and also the lungs, in which hemorrhagic pneumonitis was observed. On removing the ricin from the pomace, we were able to produce all the symptoms of experimental asthma. The experiments showed the dual nature of the castor bean seed, which contains both a primary toxic element and a purely anaphylactogenic element. Interesting instances gathered from the literature illustrate sensitization of botanists, farmers and others who handle castor bean dust, which is used as a fertilizer.

58. Figley, K. D., and Elrod, R. H.: Endemic Asthma Due to Castor Bean Dust, J. A. M. A. **90**:79 (Jan. 14) 1928.

Prausnitz [36] conducted an extensive investigation of the cotton industry in Manchester, England, as has been mentioned. He found that hypersensitiveness to cotton dust protein was regularly present in cotton operatives who were suffering from respiratory disease. In healthy cotton operatives similarly exposed the reaction was inconstant. It is interesting that 1 normal subject was artificially sensitized through an intracutaneous injection in the way that Simon and Rackemann [41] demonstrated with guinea pig serum and Hooker,[59] Park [60] and Tuft [61] with diphtheria toxin-antitoxin serum.

The active principle in cotton is derived from the dust protein of the husks; reactions were obtained with this material in a 1 : 100,000 dilution, whereas the protein from the cotton seed reacted only in a 1 : 10,000 dilution. No protein or reactions were obtained from the fiber. Prausnitz attributed a primary toxicity of the material to a histamine-like substance. Haworth and MacDonald [62] found that the histamine content of the blood of cotton operatives was higher than that of normal persons. This histamine-like substance is believed to be derived from molds which always contaminate cotton bales, much as Pediculoides infested the grain and mites infested the oat. Prausnitz, however, did not attribute the sensitization to the primary toxic substance, which may actually have been gossypol, but showed that it was due to the protein in the cotton dust.

It is of great interest to observe that most of the workers acquire their asthma after working in the cotton gins for many years, yet some, perhaps with a greater susceptibility, acquire the disease in a shorter time. Still others work a lifetime at the occupation but remain immune.

It is truly remarkable that the experiments with the inhalation method on the guinea pig should be so closely paralleled by experiments on human beings, either planned or fortuitous.

COMPARISON OF THE PATHOLOGIC PICTURE OF ASTHMA IN HUMAN BEINGS WITH THAT OF EXPERIMENTAL ASTHMA IN GUINEA PIGS

As demonstrated in the preceding pages, the shock reactions observed in the animal after inhalation of specific antigens are as a rule sublethal,

59. Hooker, S. B.: Human Hypersensitiveness Induced by Very Small Amounts of Horse Serum, J. Immunol. **9**:7, 1924.

60. Park, W. H.: Human Hypersensitiveness to Whole Horse Serum or Serum Globulins Following Diphtheria Toxin-Antitoxin Injections—Its Importance, J. Immunol. **9**:17, 1924.

61. Tuft, L.: Serum Sensitiveness After Toxin-Antitoxin, J. Allergy **3**:235, 1932.

62. Haworth, E., and MacDonald, A. D.: On Histamine in Cotton Dust and in the Blood of Cotton Workers, J. Hyg. **37**:234, 1937.

resembling in all respects the shock reactions in the asthmatic patient. There are occasional deaths of guinea pigs shocked through the inhalant route. In such animals the lung is typical of injectant anaphylaxis (fig. 2), and the antigen may have been absorbed directly into the circulation. This suggests that the pathologic changes associated with sublethal inhalant allergy must differ in some respects from those which accompany injectant allergy and may be accounted for by the direct local contact of the antigen with the sensitized tissues of the bronchi, bronchioles and alveoli (Arthus-like phenomenon). The regional sensitization demonstrated in Ulrich's [16] experiments and in our experiments with dry antigens also seems to corroborate such a hypothesis.

This leads to one of the existing controversies. Some have held that anaphylaxis in guinea pigs and asthma in human beings are not identical because the pathologic changes differ. The error of this conclusion, we believe, is due to the comparison of bronchiolar constriction with the pathologic conditions in the human being with chronic asthma. It would thus have to be admitted that Meltzer's [63] early correlation of guinea pig anaphylaxis and human asthma was not entirely justified. Acute anaphylactic death in the guinea pig can strictly be compared only with acute anaphylactic death in the human being as described in the reports of Boughton [64] and others, in which instances the lungs were completely emphysematous, owing to bronchoconstriction.

On the other hand, if the pathologic changes of asthma are compared with those found in guinea pigs subjected to repeated inhalations of specific antigens, then only are similar phases of the allergic phenomenon being considered: namely, chronic allergic respiratory states in both cases.

Pathologic Picture of Human Bronchial Asthma.—First will be considered the features of human asthma, ably described by Huber and Koessler [65] and later by Kountz and Alexander,[66] Steinberg and Figley [67] Harkavy,[68] Rackemann,[69] Wright,[70] Steinberg,[71] MacDonald,[72] Michael

63. Meltzer, S. J.: Bronchial Asthma as a Phenomenon of Anaphylaxis, J. A. M. A. **55**:1021 (Sept. 17) 1910.

64. Boughton, T. H.: Anaphylactic Death in Asthmatics, J. A. M. A. **73**: 1912 (Dec. 27) 1919.

65. Huber, H. L., and Koessler, K. K.: Pathology of Bronchial Asthma, Arch. Int. Med. **30**:689 (Dec.) 1922.

66. Kountz, W. B., and Alexander, H. L.: Death from Bronchial Asthma: Report of Three Cases, Arch. Path. **5**:1003 (June) 1928.

67. Steinberg, B., and Figley, K. D.: Pathology of Asthma: Non-Bacterial Allergic and Bacterial Types Based on Autopsy Material, J. Lab. & Clin. Med. **13**:921, 1928.

68. Harkavy, J.: Observations on Fatal Bronchial Asthma: A Report of Two Cases, J. Allergy **1**:136, 1929.

(Footnotes continued on next page)

and Rowe,[73] Gaddum,[74] Thieme and Sheldon [75] and others. Briefly stated, the pathologic picture in patients dying from asthma comprises the following changes:

1. Emphysema, lobular or universal
2. Edema of the bronchial wall
3. Sacculation of the epithelial layer of the bronchi
4. Hypertrophy of the bronchial musculature
5. Thickening and hyalinization of the basement membrane of the medium-sized bronchi and occasionally of the bronchioles and large bronchi
6. Increase of mucus in the bronchial and glandular lumens and mucous plugs in the large and medium-sized bronchi
7. Hyperplasia and hypersecretory activity of the goblet cells of the bronchi and mucous glands
8. Degenerative changes of the cartilage cells of the bronchi
9. Eosinophilic infiltration of the bronchial wall, peribronchial tissues, subepithelial layers and, at times, the bronchial lymph nodes and alveoli
10. Bronchial and bronchiolar stenosis caused by the exudative and bronchomuscular systems

Thieme and Sheldon discovered that in cases of prolonged intermittent asthma in which death resulted from some intercurrent disease the pathologic pulmonary features were never in toto those of status asthmaticus. The one constant indication of previous asthma observed in the lungs was the hyaline thickening of the basement membrane.

Pathologic Picture of Experimental Asthma.—[76] To Busson [14] must go the credit not only for successfully initiating the inhalation experiment in 1911 but for presenting a comparative study of the pathology

69. Rackemann, F. M.: Fatal Asthma—Report of a Case with Autopsy, Boston M. & S. J. **194**:531, 1926.

70. Wright, C. B.: Death from Bronchial Asthma, J. A. M. A. **94**:1218 (April 19) 1930.

71. Steinberg, B.: Recognition of the Allergic State by Tissue Examination, Am. J. Clin. Path. **4**:169, 1934.

72. MacDonald, I. G.: Local and Constitutional Pathology of Bronchial Asthma, Ann. Int. Med. **6**:253, 1932.

73. Michael, P. P., and Rowe, A. H.: Pathology of Two Fatal Cases of Bronchial Asthma, J. Allergy **6**:150, 1935.

74. Gaddum, J. H.: Monographien zur Pharmakologie und experimentellen Therapie, Leipzig, Georg Thieme, 1936, vol. 1.

75. Thieme, E. T., and Sheldon, J. M.: A Correlation of the Clinical and Pathologic Findings in Bronchial Asthma, J. Allergy **9**:246, 1938.

76. We did not have the facilities to make complete pathologic studies on our animals.

of anaphylactic death from intravenous injection and the pathologic-physiologic changes which ensue when animals manifest anaphylactic reactions to repeated sprays of antigenic liquid. In an animal killed by an intravenous injection, Busson found exclusively the markedly distended alveoli resulting from bronchoconstriction. A similar pathologic condition of the lungs was found in animals that died from a single spraying.

After repeated sublethal reactions the first effect is bronchial spasm, which leads to dilatation of the alveoli and local hyperemia of the capillaries. This action is followed by edema in the alveoli and smaller bronchi, with increased secretion of mucus and perivascular infiltration of mononuclear cells.

Busson expressed the belief that the edema in the lungs is not incompatible with anaphylaxis. The stenosis observed in the guinea pig and in the human being with bronchial asthma is therefore not exclusively the result of bronchial spasm in conjunction with edema of the mucosa and submucosa, which he correlated with the changes observed in the sublethal inhalation reactions of guinea pigs.

In 1937 Kallos and Pagel [9] went much further in the pathologic study of experimental asthma. They not only studied a group of allergically sensitized animals which inhaled sprayed antigen, but they drew a fine distinction between the conditions noted in such a group and those of a group treated with histamine and acetylcholine.

In the group treated with histamine and acetylcholine the changes in the lung were noncharacteristic. Besides chronic bronchitis, the most evident effects were the activation of the perivascular macrophages and the indications of severe disturbance of the circulation. Eosinophils played a certain but entirely subordinate role.

However, in the sprayed allergic animals, even after a single exposure, there was an enormous influx of eosinophils in the peribronchial and submucous vessels of the bronchi. At the site of the most marked migration of eosinophils were masses of mucous spheres, which increased in size and were then cast off into the lumen. The alveolar septums as well contained little nodules which consisted exclusively of eosinophils; these might completely fill the alveoli and present a picture of eosinophilic pneumonia. Besides these masses of eosinophils, there were marked edematous swellings in the walls of the smaller bronchi and in the alveolar septums; the basal membrane was thickened. Disturbances of the air content of the lung parenchyma were produced by these changes in the bronchi. Atelectasis was often combined with infiltration and splenization, together with variable emphysema. In general the histologic changes in the animals were more marked the more often attacks had been produced.

Aside from the marked aggregation of eosinophils observed in the spleen in many cases, there were no interesting changes in the other organs of this group. Even the circulatory system was untouched. The latter observations are of particular interest, because in asthmatic patients the heart is signally free from involvement (Kountz and Alexander). MacDonald, Michael and Rowe also observed that in human beings the only organ other than the lung which contained eosinophils to any extent was the spleen.

Kallos and Pagel concluded that the changes observed in the group of allergic animals after inhalation corresponded to those observed in the few reported cases of chronic bronchial asthma in human beings in which autopsies were obtained. The principal changes in human beings —the enormous eosinophilic reaction, the mucous formation which develops into mucous degeneration, the swelling of the bronchial wall and of the basement membrane and finally the secondary effects on the lung tissue, atelectasis, emphysema and infiltration, which result in the thickening of the pulmonary framework—also develop in the experimental animal.

Kallos and Pagel stressed the importance of eosinophilia in experimental asthma; similarly, Huber and Koessler stated that the chief cellular symptom of the allergic reaction in human beings is eosinophilia. In only one disease, bronchial asthma, does eosinophilia occur simultaneously in the blood, sputum and tissue, and the eosinophilic infiltration of the bronchial wall in asthma is a characteristic histologic criterion. Kountz and Alexander suggested that there is a special attraction between bronchial muscles and the specific allergens of asthma which results in excessive localization of eosinophils in and around such muscles.

The pathologic changes observed by Prausnitz [36] in animals that were subjected to prolonged exposures to cotton dust differ so definitely from those of animals dying in acute anaphylaxis that they are worthy of recital.

> The changes produced by inhalation of the dust were very pronounced. In a normal animal, sections of the lung show a typical reticulated appearance, the interalveolar walls are delicate and thin. In the dusted animals early changes, appearing after about a month, consisted in scattered peribronchial nodules. Soon after, the nodules spread and coalesced forming a peculiar thick network of the lung tissue. Instead of the string-bag appearance, there now was that of a section through a thick rubber sponge. The alveoli, on the whole, remained patent in most of the animals, but there was a great thickening of the alveolar walls. This appeared to be due in part to edema, in part to infiltration with leukocytes and dust cells. In the animals which had been dusted for six months or more, practically the entire lungs had undergone this change. In addition, localized patches of chronic pneumonia were found in some of the animals, although, during their life time, pronounced signs of illness had not been observed. Under a higher magnification, the thickened alveolar walls were found to contain a large number

of polymorphonuclear leucocytes, very many dust particles, and a small or moderate number of dust cells. They determined that histamine played a minor role and believed that cotton dust has a great power of penetrating into the deepest parts of the lungs and of producing in them very extensive irritative changes.

This study is the first to give some idea of what may actually happen to human beings after contact with antigenic dusts for long periods. Prausnitz was unable to obtain any human material post mortem. It is a pity that he did not give a more detailed picture of the basement membrane, of eosinophilic infiltration, of the mucous membrane and of the musculature of the bronchioles and bronchi.

The pathology of acute anaphylaxis in the guinea pig as discussed by Doerr [55] is of great interest when compared with the pathology of sublethal conditions after repeated inhalations.

> Bronchial stenosis may depend on a spastic contraction of the smooth bronchial musculature or on a swelling of the bronchial mucous membrane due to a suddenly appearing edema. . . . The arguments by which P. Schmidt sought to refute "the hypothesis of bronchial spasm" and to support the theory of initial bronchial edema are not tenable and in part are not in harmony with the reports of other authors. Still, it is correct that bronchial mucus plays an important role in the development of bronchostenosis and that we do not have to think of a simple ring form constriction of the bronchioles by mere muscular contraction. The bronchial mucosa does not lie smoothly on the inner wall of the bronchi in the guinea pig but forms longitudinal folds which are seen, on cross section, as villiform projections; the loose submucous cell tissues, under certain circumstances, allow these folds to be removed from the substratum; they are drawn together until they touch, and here a kind of valvular stoppage can arise which all the more forces the inspiratory movements, conditioned by air hunger, to try and overcome this. But such a conception does not force one to deny that the primary process is a muscular spasm and to assume instead that it is edema (which cannot be demonstrated anatomically either in the bronchi or in the lung tissues if the condition is uncomplicated).

Roentgen Studies on Guinea Pigs.—Kallos and Pagel found that before and during the dyspneic attacks roentgen observation of the lungs filled with iodized poppyseed oil showed that in an attack there was occlusion of the middle bronchi [77] and acute, high grade emphysema. The bronchial occlusion was conditioned by the bronchial spasm, by swelling of the bronchial mucous membrane and by plugs of secretion.

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77. W. H. Schultz and H. E. Jordan (Physiological Studies in Anaphylaxis: III. A Microscopic Study of the Anaphylactic Lung of the Guinea Pig and Mouse, J. Pharmacol. & Exper. Med. **2**:375, 1911) showed that in anaphylactic shock in the guinea pig the bronchial stenosis is high, occurring in the secondary and tertiary bronchi, with practically no involvement of the smaller bronchioles. Because of the cartilaginous areas, it is difficult to conceive of occlusion of the larger air passages in a human being as a result of the constriction of muscle fibers. It is more probable that the muscular constriction is situated farther out in the bronchial tree, particularly in the bronchioles, where there is an absence of cartilage and a relative increase in the size of the muscles.

Roentgen Studies on Human Beings.—Steinberg [78] correlated the roentgen and the postmortem observations and commented as follows: "It may be assumed that an attack is ushered in by bronchospasm, but all the evidence is against bronchoconstriction being responsible for the entire trend of events preceding and following the peak of an attack." He stated the belief that an asthmatic paroxysm is essentially due to bronchial occlusion by mucus as a result of hypersecretory activity of the bronchial mucous glands.

Rigler and Koucky [79] made a roentgen study of the bronchi of asthmatic patients by means of iodized oil. In early stages, the caliber of the bronchi was distinctly narrowed. Later some of the bronchi failed to show the shadows of iodized oil, which indicated that occlusion had taken place. The authors concluded that the first effect is due to spasm of the bronchial muscle. Mucus accumulates within the lumens of the bronchi. A plug is formed, partially obstructing the bronchus so that air may be inspired past the occlusion but is expelled less rapidly. Emphysema is thus produced. During the asthmatic attack the spastic bronchial muscle clamps down around this plug, aggravating the occlusion.

Involvement of the Exudative and the Bronchomuscular System.—It becomes apparent, then, that death in a human subject resulting from an injection of serum may be likened to anaphylactic death in the guinea pig, caused by injection, but the pathologic changes in bronchial asthma must be compared with the secondary changes observed by Busson, by Kallos and Pagel and by Prausnitz in guinea pigs which were subjected to repeated inhalation. The observations of Huber and Koessler and of Kallos and Pagel make it plain that in human beings as well as in guinea pigs the allergic reaction of the tissues is not confined alone to the smooth muscle fiber system but involves the whole organic system which serves exudative processes of endothelium, epithelium, capillaries and glands. The rational attitude toward the question, it appears, is to realize that the exudative and the bronchomuscular system act simultaneously in the production of stenosis; in some cases one is more concerned than the other, but always both are involved to some extent.

CONCLUSIONS

Guinea pigs exposed to a dry antigenic dust are sensitized with great frequency if the exposure is adequate. Five to seven hours seems to be the optimum period.

78. Steinberg, B.: Mechanism of an Asthmatic Attack in Chronic Allergic Asthma, J. Allergy **3**:139, 1932.

79. Rigler, L. G., and Koucky, R.: Roentgen Studies of the Pathological Physiology of Bronchial Asthma, Am. J. Roentgenol. **39**:353, 1938.

Animals sensitized by inhalation have attacks of asthma of varying degrees of severity when subsequently exposed to the specific dust. For the most part, they react each time they are exposed and do not manifest the classic antianaphylactic state observed after repeated parenteral injection. However, in some animals the response is not constant and refractoriness is observed during some exposures. This train of events resembles the sequence of attacks in human bronchial asthma and in status asthmaticus.

Certain animals appear to remain unaffected in spite of repeated exposure. Whether this resistance is relative or absolute we are not prepared to state. As the source of supply and the factors of weight, age, type of exposure and nature of the antigen were the same, the differences exhibited by the animals, with respect to the readiness and rapidity with which sensitization was established and the severity of their reactions, appear to be due to the amount of exposure and to certain inherent attributes of the individual subjects.

Although the experiments reported here are not sufficiently extensive to permit final conclusions, it appears that when the sensitizing agent is a dry antigenic dust sensitization may be regional, involving the respiratory structure alone, or may be more extensive, involving other organs. The regional condition is comparable, we believe, to human inhalant allergy with negative endermal reactions.

The pathology of sublethal inhalant allergy, which differs materially from the pathology of injectant allergy, may be accounted for by the direct local contact of the antigen with the sensitized tissues of the bronchi, bronchioles and alveoli.

The pathologic processes causing anaphylactic death cannot be compared with those of bronchial asthma. When the pathologic changes of asthma are compared with those observed in guinea pigs subjected to repeated direct inhalations of specific antigens, there is actually comparison of similar phases of the allergic phenomenon—namely, chronic allergic respiratory states in both cases. It is seen that the changes are fundamentally indistinguishable in the two conditions.

The described method of studying experimental asthma in the guinea pig, which we believe closely parallels human inhalant asthma and pollinosis, offers wide possibilities for detailed investigation of phylactic and prophylactic measures relating to these syndromes in the human subject.

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STUDIES IN IMMUNITY

VI. SPONTANEOUS CHANGES IN THE DICK AND SCHICK REACTIONS OF CHILDREN

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AND
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Both immunity to scarlet fever and immunity to diphtheria as measured by cutaneous reactions vary from time to time. We have observed the frequency with which negative reactions become positive over a period of years in several groups of children. This study constitutes a continuation of our previous reports on factors which affect cutaneous reactions.[1]

PROCEDURE

Our purpose was to examine normal variations of cutaneous reactions, uninfluenced by the immunity which may be produced by disease or by artificial immunization. At intervals of one or two years the entire populations of several orphanages were tested with Dick and with Schick toxins. All of the children who had positive reactions were subsequently given injections of immunizing agents and were therefore no longer included in the study. Children whose original tests gave negative results were retested from year to year, and the spontaneous reversals[2] in this series of children are here recorded. The children in some of the institutions had been under observation since birth, so that their entire medical history was known. In other institutions the children had not been admitted until they were 4 or 5 years of age or even older; under these conditions we accepted the previous history that there had been no attack of scarlet fever or of diphtheria and no artificial immunization against these diseases.

From the Department of Pediatrics, University of Cincinnati, and the Children's Hospital Research Foundation.

1. Wherry, W. B.; Eddy, B. E.; Mitchell, A. G., and Stevenson, F. E.: Effect of Various Diseases on the Sensitivity of the Tuberculin Test, Ohio State M. J. **25**:199-201 (March) 1929. Eddy, B., and Mitchell, A. G.: Studies in Immunity: II. Effect on the Skin Tuberculin Reaction of Nonspecific Factors, Am. J. Dis. Child. **40**:771-775 (Oct.) 1930; III. Effect of Diseases Other Than Diphtheria on the Schick Test, ibid. **40**:985-987 (Nov.) 1930; IV. Effect of Diseases Other Than Scarlet Fever on the Dick Test, ibid. **40**:988-992 (Nov.) 1930. Mitchell, A. G.; Nelson, W. E., and LeBlanc, T. J.: Studies in Immunity: V. Effect of Acute Diseases on the Reaction of the Skin to Tuberculin, ibid. **49**: 695-702 (March) 1935.

2. The phrase "spontaneous reversal" is used to denote a change of the cutaneous reaction from negative to positive.

The variations in reactions reflect to a certain extent the many possible errors of technic in performing the tests,[3] differences in potency of the material employed, difficulties in the interpretation of the reactions and incorrect use of syringes.[4] An attempt was made to reduce these several sources of error to a minimum by having all of the tests performed by the same investigator (R. A. L.) or under his close supervision. Materials were freshly diluted, and all reactions were observed under proper light. Reactions greater than 5 mm. in any diameter were considered positive.

RESULTS

Table 1 shows the subsequent course of the Dick test in the negative reactors of school age, i. e., 5 to 16 years, and table 2, the course in negative reactors of preschool age, i. e., 1 to 4 years. Whenever a positive

TABLE 1.—*Changes Occurring in Negative Dick Reactions in Children of School Age*

Period After First Test, Yr.	Number of Subjects	Percentage with Negative Reactions	Percentage with Positive Reactions
0 (original group)	641	100	0
1	177	91.5	8.5
2	474	73.8	26.2
3	111	93.7	6.3
4	165	90.9	9.1
5	15	100	0
6	6	83.3	16.7

TABLE 2.—*Changes Occurring in Negative Dick Reactions of Children of Preschool Age*

Period After First Test, Yr.	Number of Subjects	Percentage with Negative Reactions	Percentage with Positive Reactions
0 (original group)	53	100	0
1	53	84.9	15.1
2	34	91.2	8.8
3	29	100.0	0
4	0	....	....
5	16	100.0	0

reaction developed during the period of observation, the result was recorded; the child was immediately given injections of scarlet fever toxin, and therefore his subsequent course was not included in the series reported here.

These tables show that 8.5 per cent of 177 children of school age whose Dick reactions were negative had positive reactions one year later; 26.2 per cent of 464 children of school age whose Dick reactions were negative had positive reactions two years later. Three and four

3. Dick, G. F.: Scarlet Fever, with Consideration of Other Haemolytic Streptococcus Infections, Internat. Clin. **1**:150-176 (March) 1930. Dick, G. F., and Dick, G. H.: Local Immunity to Scarlet Fever Toxin, J. Infect. Dis. **62**:83-87 (Jan.-Feb.) 1938.

4. Nelson, W. E.; Seibert, F. B., and Long, E. R.: Technical Factors Affecting the Tuberculin Test, J. A. M. A. **108**:2179-2181 (June 26) 1937.

years later the percentages of spontaneous reversals were 6.3 and 9.1, respectively. The groups observed for longer periods than two years were so small that little importance can be attached to the results.

The number of nonimmunized children of preschool age with negative Dick reactions was small; only 53 belonging in this category could be found in the institutions examined. At the end of one year 15.1 per cent had become positive reactors; of 34 negative reactors who were tested at the end of two years, 8.8 per cent had become positive; of 29 tested at the end of three years, none had become positive.

The percentage of subjects who showed reversal of the Schick test from negative to positive is shown in table 3.

This table shows that 12.6 per cent of a group of 190 children with negative Schick reactions had positive reactions a year later; 16 per cent of 243 negative reactions in children reverted to positive in two years, and 4.7 per cent of 255, in three years.

TABLE 3.—*Changes Occurring in Negative Schick Reactions of Children of School Age*

Period After First Test, Yr.	Number of Subjects	Percentage with Negative Reactions	Percentage with Positive Reactions
0 (original group)	453	100	0
1	190	87.4	12.6
2	243	84.0	16.0
3	255	95.3	4.7
4	0	....	....
5	10	90.0	10.0

COMMENT

In three of the groups reported on in this paper no instance of scarlet fever was seen in those with negative Dick reactions during the five year period in which repeated examination and inoculation of the susceptible children were carried out. In one of the institutions for infants and young children scarlet fever was introduced by an adult attendant. All of the children with negative Dick reactions escaped the infection, but 2 children whose reactions originally were negative but subsequently were faintly positive had mild attacks of the disease. In another instance, the son of the superintendent of one institution was the only child of the group not tested and not given injections of toxin. He subsequently contracted scarlet fever from an outside source, and none of the inhabitants of the institution who had been given injections had the infection. It is possible that sore throats without erythematous rashes occurred (subclinical scarlet fever), but if this was true the disease was mild, and no complications of a scarlatinal nature occurred.

It seems logical to conclude that repetition of Dick and Schick tests at intervals of one or at most two years is necessary if one is to be sure that a person's immunity has persisted. The suggestion has been

made that, rather than test a child frequently, one may give an injection of the immunizing agent every two or three years during the first six years of life. This procedure will usually raise the antibody titer to levels well above the minimum considered necessary for protection.

SUMMARY AND CONCLUSIONS

Repeated Dick tests in several large institutions showed that in children of school age about 8 per cent of the spontaneously negative reactions became positive after one year and about 26 per cent after two years. In children of preschool age with negative reactions there was spontaneous reversal to positive in one year in about 15 per cent and in two years in about 9 per cent.

Negative Schick reactions in children of school age became positive at the rate of about 13 per cent after one year and 16 per cent after two years.

Technical errors may account for some of the variations in cutaneous reactions, but it is probable that the antibody titers of children fluctuate from time to time and frequently fall below protective levels.

Dick and Schick tests should be repeated at intervals of a year in order that it may be ascertained what children need immunizing injections; thus maximum protection against scarlet fever and diphtheria will be assured. The plan of administering the immunizing agent every two or three years during the first six years of life, regardless of the cutaneous test, appears to be highly desirable.

Drs. John C. Danahy, Thomas Humphrey, Ernest Ekermeyer and Mendel Zeligs cooperated when these studies were carried out in the several institutions.

FACTORS INFLUENCING DEVELOPMENT OF SEXUAL ATTITUDES AND SEXUAL AWARENESS IN CHILDREN

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The student of human sexual behavior is becoming more interested in the average child as he actually thinks, feels and acts. He is asking for facts directly supplied by children as well as about children. This is in direct contrast to the attitude which existed before the turn of the present century. During the former period the sexual attitudes and sexual awareness of children were referred to in terms of "degeneracy" or "perversion" or were presented as examples of precocious development of a hypothetic sex instinct.

The present day investigator has developed methods for meeting the child on his own level of spontaneous interest in sex and day to day awareness of sexual topics. This has been made possible despite the fact that in present day culture children at an early age become aware that certain topics may not be mentioned, that particular parts of the body may not be referred to or displayed and that, not infrequently, they are instructed not to repeat to outsiders any information on sex which is given to them. In many cases they are given either no name by which to designate the sexual organs or one of fanciful origin, and much to their confusion they discover that there are a number of terms applied by other children to these regions of the body. Such experiences sensitize children to the topic of sex, and when parents become embarrassed and frankly critical of such utterances, there are established patterns of sensitivity to any inquiry touching on sexual attitudes.

Nevertheless, the investigator can begin to collect objective data when the child is given an opportunity to express himself by means of a play interview,[1] during which the child can speak of a boy or a

This study was made possible by a grant from the Child Neurology Research (Friedsam Foundation).

From the Children's Psychiatric Clinic of the Harriet Lane Home for Invalid Children, Johns Hopkins Hospital.

Part of this material was presented at the Fiftieth Anniversary Institute of the Child Study Association of America, Nov. 16, 1938, New York.

1. Conn, J. H.: The Child Speaks to the Psychiatrist: Introduction to the Method of the Play-Interview, Occup. Therapy **17**:231 (Aug.) 1938; The Child Reveals Himself Through Play: The Method of the Play-Interview, Ment. Hyg. **23**:49 (Jan.) 1939.

girl doll as if the doll and not he himself were discussing various sexual topics. Such material indicates the manner in which children utilize the sexual information that they have received and the way they begin to transform this data into what are termed adult, mature conceptions of sexual functions and processes.

What is included under the topic of sex for the average child? The material offered by children indicates that one must take into account what the arrival of a new baby in the home or neighborhood means to the child as well as the manner in which he accounts for the physical changes in the pregnant mother. The initial attempts at self observation and self exploration, coming at the time when the child is getting acquainted with his body and its functions, his exploration of the bodies of other persons and the attitudes that develop from these experiences should be studied. The spontaneous sexual questions of the child, which represent both a reaching out for help and a testing of his own formulations, must be taken seriously. In addition, the dreams of children should be collected in order to determine at what ages they begin to dream about members of the opposite sex. Early patterns of courtship and the types of sexual play and sexual talk that actually occur in the neighborhood, as well as the facts contributed by the movies and the radio, play their part.

The material should be viewed from the perspective of the child's life history, with physical, intellectual and emotional factors being taken into account. It should include a record of his opportunities for experimentation and of the parental attitude toward sexual instruction and an interpretation of parent-child relationships. Such a study is under way at the Children's Psychiatric Clinic, which is conducted by Dr. Leo Kanner at the Harriet Lane Home, Johns Hopkins Hospital. Two hundred children from 4 to 12 years of age have been examined at regular intervals over two years as part of a research project.

When the data collected in this manner are scrutinized, certain factors appear as having influenced children's sexual attitudes. The first of these may be discussed as the contribution made by language itself.

At an early age the child becomes sensitized to certain words. He has been admonished not to say them, and he has heard the embarrassed laughter of children and adults or has seen them look askance whenever these words are spoken. It is not the thing itself but its symbol which appears dirty or sinful and gives rise to the feeling of shame.

The average child of 5 or 6 who has had an opportunity to observe genital differences can say that the boy has "a straight one and the girl ain't," that "girls have short ones and boys have long ones," or that a boy's "sticks out and a girl's doesn't." This is as much a fact as any other fact which the child has experienced, and he can report what

he has seen without any feeling of embarrassment. It is the name or label that he has great reluctance in divulging.

This name may be as innocent as the terms "kisser," "peanut" or "woozle." It may be as innocuous as the words "dewdrop," "Teddy bear," "dickybird," "train," "piece of string" or "bottom." Nevertheless, the child becomes restless, bites his lips or hangs his head and refuses to speak when he is requested to utter the word which refers to that particular part of the body. Thus Richard, aged 5, said: "A girl has a different thing. I don't want to say it 'cause it might be a bad word. You go to the bathroom and make pee-pee with it." Harriet, aged 8, stated: "The girl's body is different from the boy's. I know what you call it, but I don't want to say it." But she freely discussed her experiences, saying: "Mother and Daddy undress in front of me. Daddy's is more long than anything. Mother's is short and mostly round." She finally permitted a girl doll to whisper the forbidden word into the ear of another doll. It was the term "pocketbook." Harriet knew that "there is another word for it." She said: "I won't say it because it's bad. It doesn't sound nice and it isn't nice to say." The word is "picturegarden." At 6 years of age, Harriet made the observation: "Mother has a picturegarden. Peggy (her sister) has one and I have. Daddy has one, too, but it's a funny one." She repeatedly had heard her mother say: "Put down your legs or people will see your picturegarden!"

The second factor is age. The educator and his colleague, the psychologist, have taken as their fundamental assumption that the child should begin by learning the facts that he can grasp and make his own before undertaking more complex tasks. The 5 year old child is not taught how to handle fractions or how to master the decimal system. He is assigned lessons in keeping with his age and capacity for comprehension. What happens in the case of sexual instruction? The average mother decides that it is time to tell the child the "facts of life." She may answer the question "How do we get babies?" with the analogy of the seed or the flower. She may even make a noble attempt and say: "The seed is planted in the mother by the father."

What about the child? When does he begin to understand such a formulation and how much of it does he recall several years later?

Earl was 4 years and 6 months of age when he asked about babies and was told that they come from seeds, like flowers and trees. At 5 years and 6 months of age he asked: "Where do seeds come from?" and was told that they are planted in the mother by the father. At 6 years of age he asked: "Do chickens come from seeds?" and was told about eggs. At 7 he asked if rabbits come from eggs. How much of this information did he recall when he was interviewed at the age of 8? He now said: "The mother gets the baby at the hospital. God

made it from other people's bones." He wanted to know: "How can the hospital find a place for another baby, and how do they know when a baby is coming?" Another noble experiment has failed. This child was presented with concepts of seeds growing in the body before he could grasp the significance of such a formulation and make it his own.

The number of questions that a child asks concerning sexual topics may not be as significant as his purpose in seeking this information. The mother who is focusing her attention on the information itself or on performing her duty in a matter-of-fact manner may forget that the sexual information which she furnishes may be exchanged for other sexual facts, fancies and misconceptions. The possession of sexual information is one of the proofs which the child utilizes in demonstrating to others that he is growing up.

David was 5 years old when he asked: "Where do babies come from?" He was told about the seeds that are planted in the mother. He insisted on knowing how the seeds got into the mother and was informed that God puts the seeds there. He then wanted to know how God put them there. When he was put off, he exclaimed: "I know, they swallow them!" He then asked: "How do they grow into a baby?" and was told: "It takes a long time. It's like planting a seed in the ground." He followed this up by asking: "How do you know it's ready to come out?" The mother replied: "You feel it's moving around, and you know the baby wants to come out." David went on to inquire: "How does it come out?" and was told that it comes out through the stomach. He then demanded that the mother tell it to him all over again, so that he could remember it, and when he heard the story the second time, he rushed out to tell his older brother (aged 8) all about it. He was thrilled to be the first to know about the origin of babies.

What had this child remembered at the age of 8 years? His only comment was that babies are bought at stores. The suggestion that seeds have something to do with babies recalled nothing to him. He could not reproduce any of the details of the incident which had occurred at the age of 5 years.

This account of the interest of the child in collecting sexual information because of the prestige it carries with it introduces the role of the factor of socialization.

The average child of preschool age thinks in terms of what he sees going on around him. His own experiences and the tendency on the part of the parent to misdirect his attention lead him to believe that some external agency is responsible for the coming of the baby. The pregnant mother or neighbor is thought of as having eaten too much and become "too fat." The possibility of the baby's being in the body of the mother is denied by nearly every child at this age (4 to 6 years). The child's dependence on the parent, his desire to please, his implicit

faith and his lack of contradictory experience permit him to accept the story of the stork, kindred tales of angels, birds and airplanes or the idea that the baby is bought in a store.

His own curiosity begins to point in the direction of the mother's body when he begins to talk to other children. This period of socialization occurs about the age of 7. During this period of life the child begins to ask questions about the possibility of the baby's being in the mother. He now wants to know how the baby leaves the mother's body.

Arnold, aged 7, asked: "What do they do with the children in the hospital that the mothers don't call for or buy?" At 8 years of age, he spoke of the gas on his stomach and said: "My stomach moves around like a woman who is pregnant." He now asked: "How does the baby get out of the stomach?" Edgar was 5 when he asked: "How do babies grow?" and was told that the process is like that of a flower growing from a bud. At 6, he was visited by twins and asked: "How much does a baby brother cost? Does it cost more than a sister?" He was 6 years and 8 months old when he inquired: "What is the first step to have a baby? What do *you* have to do to have a baby?" He had passed from one phase of his development to another; he no longer thought that babies are bought but vaguely imagined that in some manner they come from the body of the mother.

In the latter phase the child is beginning to explore the world beyond the family circle. He brings into this period sexual awareness derived from his earlier experiences. The child already has developed attitudes concerning the sexes. He is aware that boys not only dress differently but play differently. Boys play rough games and enjoy wrestling, boxing and climbing. Girls play with dolls and at being mothers. They speak of being afraid to engage in boys' sports for fear of being hurt. Boys think of girls as those "who can't take it" as they can, who have "sweet" voices and who like to keep clean. They boast of being able to fight girls and outrun them and ridicule their fears of the dark. In general, the child at this age thinks that boys are the "stronger" and girls are the "weaker" sex.

In addition to developing such cultural and psychosexual differentiations the child may have had specific sexual experiences. In many cases he has had the opportunity to inspect and be inspected. Girls often report that boys have attempted to undress them. Children who have voided in each other's presence and undressed before each other express themselves as wanting the members of the other sex to do likewise. Boys report that other boys have tried to get them to handle the sexual organs; all these and many other sexual incidents occur among average children.

The patterns of courtship and experimentation with interpersonal relationships are being developed in this stage of growth (7 to 9). The

child is losing many of his earlier beliefs. Formulations such as those dealing with the supposition that babies are born through the anal passage are being given up for so-called grown-up conceptions, which are obtained during discussions with older children.

Caroline, aged 9, was proud of the fact that she knew all about origins. She said: "Now I know how babies are born. They operate on the mother and get the baby out." She wanted to know: "How does the baby get in the mother?" and spontaneously replied: "By eating and then the baby gets made. The mother eats her food and then she gets operated on." This was her conception of what a grown person knows about babies after her recent discussion of this topic with her 13 year old sister. Her own account was as follows: "When I was small, I thought the mother lays down and it comes out of her backside. I really thought that before. I thought it was right. I thought the lady went to the toilet and it had to come out that way. (Why?) The lady et her food from her mouth, then it goes down her stomach to her backside. When I got bigger, my sister began telling me things. She says that the baby came out of the stomach part, so I thought I was wrong." This brief case abstract illustrates children's deference to the conceptions of older children and their interest in collecting sexual information as a means of proving that they are grown-up.

It is during this phase of socialization that the patterns of early courtship appear and dreams of the opposite sex occur. Caroline reported that her first dream of a boy occurred at the age of 8. She said that in the dream a boy (aged 10) took her out to a restaurant and then to the movies, and she added: "He kissed me and tried to say he loves me but couldn't say it. He was ashamed to say it. He don't want to tell me right away. He'd tell me later on. I couldn't dream that far. I had to wake up." At home she had been teased by her older sister about this boy friend. The mother added that this boy was shy but that Caroline kept asking him to play his favorite game and let him have his own way all of the time.

Harry, aged 7 years and 6 months, dreamed of his girl friend, Betty. He had also dreamed that Shirley Temple was living with him and that he was sleeping with her and kissing her. Harry liked to sit near Betty in school. He spoke of her as being pretty and felt happy when he walked with her. He kissed her and stated that if any one saw him, "they would make fun of me for sure."

Arnold, aged 9 years, said: "I dream I go out with a girl and buy her sodas and kiss her. I don't like to tell any one these dreams. (Why?) They make fun of me. I wouldn't want to tell my mother. She might tell everybody, and they might make fun of me. Two weeks ago I told her I had a girl friend, and she began to tell everybody and they laughed. I have lots of girl friends. Anne is my best girl friend. I dream sometimes I kiss her. I don't like to tell my mother."

This material indicates that children of both sexes begin by playing games, become attracted to one another and then dream of those they like to be with. The concept of love and marriage appears during this period (7 to 9); it is defined as wanting to live with some one all the time because he or she is "nice" or "pretty" and reciprocates this sentiment.

The fourth factor which begins to determine children's sexual attitudes and awareness can be designated by the term "sensuous." The child becomes aware of the presence of certain genital sensations which he can describe as tickling, tingling, itching or stinging. Children report that these sensations are so gratifying that their attention is repeatedly directed to the anatomic structures involved. In the material of this study parental admonitions, threats of punishment, warnings of illness or death and the actual burning of the penis in 1 case have had little effect in deterring children from such practices. The spontaneous remark of a 4 year old boy, whose mother was attempting to distract him from manipulating his genitals, may help to explain why such attempts fail. This boy exclaimed: "Oh, Mother, why don't you try it? It feels so good!"

Such practices are the child's reactions to a newly found awareness of local sensitivity. During the active phase of socialization these localized sensual feelings may become associated with imaginations of the genitals of the opposite sex. Much of the content of these imaginations is suppled by direct observation and discussion of sexual topics with other children. Thus John, aged 9, knew that "bad boys do it" (masturbate). He said: "They go in alleys and hide. They stick their hands in their pockets and fool with their pee-wee." He stated that they do it because it "tickles all the time and gets so long." His own imaginations contain references to the genitals of the opposite sex, and during the play-interview he spontaneously drew a picture of the female genital organs that does justice to his powers of observation.

The boy 10 or 12 years of age is beginning to think in terms of genital contact. He has heard about the sexual act and thinks of it in terms of some form of touching of the excretory organs. The Anglo-Saxon four letter unutterable word becomes part of his vocabulary during this phase of his development. Since he is usually uninformed about the facts of seminal emission and ovulation, he remains puzzled and formulates his own explanations. The baby already may be inside the mother's body and may fall out during the sexual act, which he thinks results in a widening of the genital orifice. One boy (aged 11) spoke of the baby as taking hold of the male genital organ and in this manner being drawn out of the mother's body. The blood of the father and mother may mix, or the father may touch off something in the excretory organ of the mother and start the growth of the baby.

Another boy (aged 10) spoke of the urine of the father mingling with that of the mother and thus forming the baby. He said that it is such "stuff" which accounts for the swelling of the mother's abdomen. The average child at this age thinks of the baby as being in the "stomach" of the mother and speaks of a surgical procedure as necessary before the baby can be removed by the doctor.

What general conclusions can be drawn from such variegated data? Progress in any field depends on the discovery of principles derived from the collection and grouping of objective facts. If physicians and parents are to collaborate in planning a graded program of sexual education, they must permit children to speak of their experiences. When such material is collected from average children, there is much ground for reassurance.

It is important for parents to know that children are not stimulated to explore their environment sexually when such topics are discussed in a matter-of-fact manner. Healthy children are not as easily upset as some theorists would lead one to believe. The viewing of the genitals of the opposite sex, the manipulation of the genitals by another child or a glimpse of the parent undressed does not disturb the average child. It does not cause him to spend a great deal of time ruminating about such events. Children pass from one experience to another, assimilating and synthesizing their sexual experiences as they do with other issues of everyday living. The material of this study does not bear out the statement that the child loses confidence in the parent who fails to disclose completely the facts of sex or that the child who is rebuffed when he asks sexual questions is led to the conclusion that "all knowledge is wicked." The child is a realist. At an early age he learns and accepts the facts that all adults have their peculiar rules and that one of these rules in some homes is that all talk of sex is forbidden. There is a tendency in present day culture to confuse a collection of terms with knowledge and knowledge with the capacity for efficient living.

Contact with other children helps to direct the sexual imaginations of the child toward heterosexuality. Overprotection and oversolicitude on the part of the parent tend to deprive the child of the opportunity of exchanging information on sex with his fellows. Such deprivations may help to retard the child's sexual orientation during this phase of active social and sexual growth.

The parent must accept the conclusion that some degree of sexual curiosity and some form of sexual experimentation are normal for the average child. The parent can learn that what is required of him is not one talk about the "facts of life" but a graded program of education on sex, beginning with an effective sexual vocabulary in the preschool years and continuing in close contact with the sexual events of everyday life.

RESPONSE TO ANTISERUMS IN MENINGOCOCCIC INFECTIONS OF HUMAN BEINGS AND MICE

A COMPARATIVE STUDY

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Since the discovery of Miller [1] that suspensions of mucin greatly enhance the virulence of meningococci for mice, the mouse protection test has been used by a number of investigators [2] as a method for titrating the protective value of antimeningococcus serums. There is general agreement that this constitutes the most satisfactory method of standardization. However, it is obvious, as will be shown by the details of the test, that such a method, because of the time and expense involved, is not applicable to the routine testing of strains prior to treatment with the serum selected. The following questions must therefore be answered before the test can be accepted as a reliable method for determining the therapeutic efficiency of the serums available at the beginning of an epidemic. If a serum produces good protection in mice against one type I strain, can one expect good protection in mice against all type I strains from a given epidemic? Is there a correlation between the protective value of a serum in mice and the therapeutic response in human beings? The work to be reported represents an attempt to answer these questions.

MATERIAL AND METHODS

Material for this study was obtained from the Baltimore meningococcic meningitis epidemic of 1936,[1] which furnished a group of patients for whom treatment was fairly well standardized. Serum was given intravenously only to the patients showing obvious clinical signs of bacteremia. Serum was given intrathecally to all patients at least once daily in amounts varying from 15 to 30 cc., according to the quantity of spinal fluid which it was necessary to remove in order to obtain normal pressure. The patients who presented severe infections received the first two intrathecal treatments at twelve hour intervals. Serum therapy was continued

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From the Department of Diseases of Children, College of Physicians and Surgeons, Columbia University.

1. Miller, C. P.: Science **78**:340, 1933.

2. (*a*) Rake, G.: Proc. Soc. Exper. Biol. & Med. **32**:1175, 1935. (*b*) Miller, C. P.: ibid. **32**:1141, 1935. (*c*) Rake, G.: J. Exper. Med. **61**:545, 1935. (*d*) Cohen, S.: J. Immunol. **30**:203, 1936. (*e*) Miller, C. P., and Castles, R.: J. Infect. Dis. **58**:263, 1936. (*f*) Mishulow, L.; Melman, M., and Sklarsky, R.: J. Lab. & Clin. Med. **21**:406, 1936. (*g*) Brown, T. M.: Bull. Johns Hopkins Hosp. **61**:272, 1937. (*h*) Rake, G.: Canad. Pub. Health J. **28**:265, 1937.

until 1 spinal fluid culture had remained sterile for forty-eight hours and 1 for twenty-four hours.

Freshly isolated cultures were dried and sealed under vacuum by the method of Brown.[3] As suggested by Brown,[4] the tubes were sealed thirty minutes after the pressure had registered 10 microns on a McLeod gage. No change in virulence was demonstrated as the result of drying. A vial of the serum with which each strain was treated in the patient was collected during the epidemic and stored at ice box temperature. During the following year mouse protection tests with the serums against the dried strains were carried out in the laboratory of the Babies Hospital. Strains from 9 patients who died and from 11 who recovered were tested in mice to determine the protective value of the serums which had been used in the patients from whom the strains had been isolated.

The protection test used was that devised by Rake.[2a] The table presents results of the test. A Gates turbidometer was used for standardizing the turbidity of the

Results of Mouse Protection Test *

	Dilutions of Organisms									
Dilutions of Serum	10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}	10^{-7}	10^{-8}	10^{-9}	Protection†
2:5, given 30 minutes before organisms	45 S	S S	S S	..	..	..	..	..	..	1,000,000
1:10, given 30 minutes before organisms	22 S	S S	S S	..	..	..	..	..	..	1,000,000
1:40, given 30 minutes before organisms	21 23	S S	S S	..	..	..	..	..	..	1,000,000
1:640, given 30 minutes before organisms	..	22 S	S S	S S	S S	..	..	..	..	100,000
2:5, given 5 hours after organisms	..	45 S	S S	S S	..	..	..	..	..	100,000
2:5, given 10 hours after organisms	..	..	22 22	23 45	45 72	S S	..	..	..	100
Controls for virulence	..	..	..	..	..	21 28	21 21	21 21	22 S	.....

* Numbers indicate hours after infection when death occurred; S indicates survival.
† Numbers indicate multiples of minimal lethal doses against which protection was secured.

saline suspension of organisms so that 1 cc. contained the dose indicated. Seven per cent mucin was found to give more consistent virulence than 5 per cent mucin. The virulence of any given strain varies widely unless certain standards are rigidly adhered to. Because of the fundamental importance of obtaining the maximum virulence of a strain, the method used will be described in some detail. The dried culture on filter paper was removed from the sealed vacuum tube and dropped into warmed rabbit blood pneumococcus broth. After twenty hours' growth two transfers to blood broth were made at twenty hour intervals. Rabbit blood pneumococcus agar plates were inoculated with the second broth transplant and incubated twelve to fourteen hours. This culture was washed off with an 0.85 per cent solution of sodium chloride and diluted so that 1 cc. contained 2,000,000,000 organisms. The standardization of the suspension by a Gates turbidometer was completed in less than ten minutes in order that the meningococci might be removed from the sodium chloride environment, which has a deleterious effect over longer periods. This standard suspension was used in making the dilutions in 7 per cent

3. Brown, J. H.: Science **64**:429, 1926.
4. Brown, J. H.: Personal communication to the author.

mucin; these ranged from 10^{-1} to 10^{-9}, inclusive. The mucin dilutions were injected as soon as possible after preparation for both the virulence test and the mouse protection test. The dilutions of serum used for protection at the various time intervals are listed in the vertical column. Each dilution of serum in saline solution was given in doses of 0.5 cc. per mouse. Two mice were used for each combination of dose of organisms and serum dilution, a total of 46 mice being used for the test. A preliminary virulence test was performed on the previous day and was repeated as a control for the protection test. The virulence of all strains from patients who died and from those who recovered was remarkably

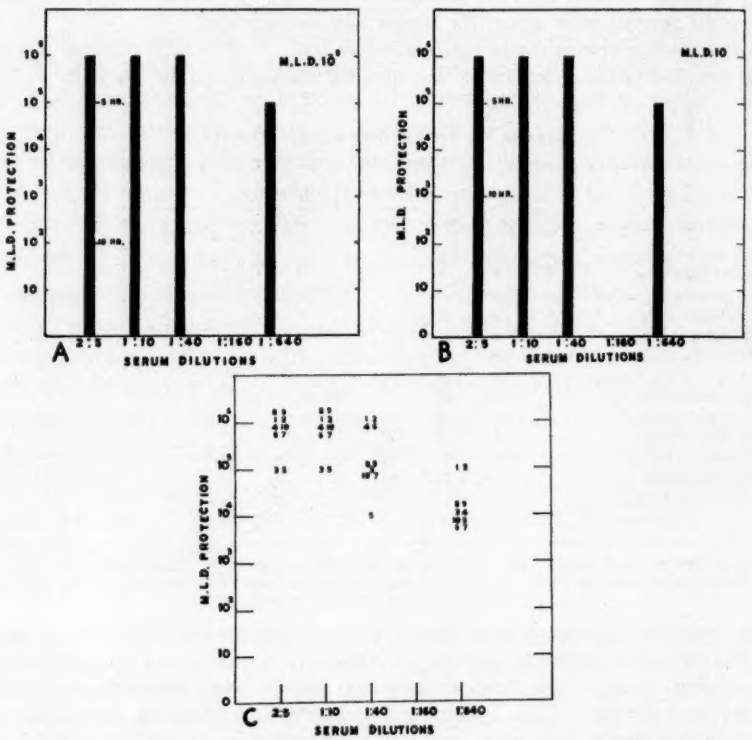

Chart 1.—*A*, protection obtained by the unconcentrated commercial serum against a single strain from a patient who died. *B*, protection obtained by the unconcentrated commercial serum against a second single strain from a patient who died. *C*, composite representation of 10 protection tests using the commercial serum against 10 different strains.

constant, 20 organisms being lethal in all but 3 instances. In 2 of these, 200 organisms, or 1 cc. of the 10^{-7} dilution, represented the minimal lethal dose, and in the third, 2 organisms, or 1 cc. of the 10^{-9} dilution. The protective value of each dilution of serum was calculated in terms of protection against multiples of the minimal lethal dose.

Of the 20 strains tested, 10 were isolated from patients treated with a commercial unconcentrated serum, 3 from those treated with New York state

unconcentrated serum and 7 from those treated by New York state concentrated serum. These same combinations of strains of organisms and serums were used in the mouse protection tests. Graphic representations demonstrate the protection obtained against 2 different strains with each of 3 types of serum used (charts 1 *A* and *B*, 2 *A* and *B*, 3 *A* and *B*). The scales of all charts have been kept constant. The various dilutions of serum, each represented by a column, are charted on the abscissas; multiples of the minimal lethal dose against which these dilutions protected are charted on the ordinates. The height of each column represents the protection obtained when the serum was given thirty minutes before the

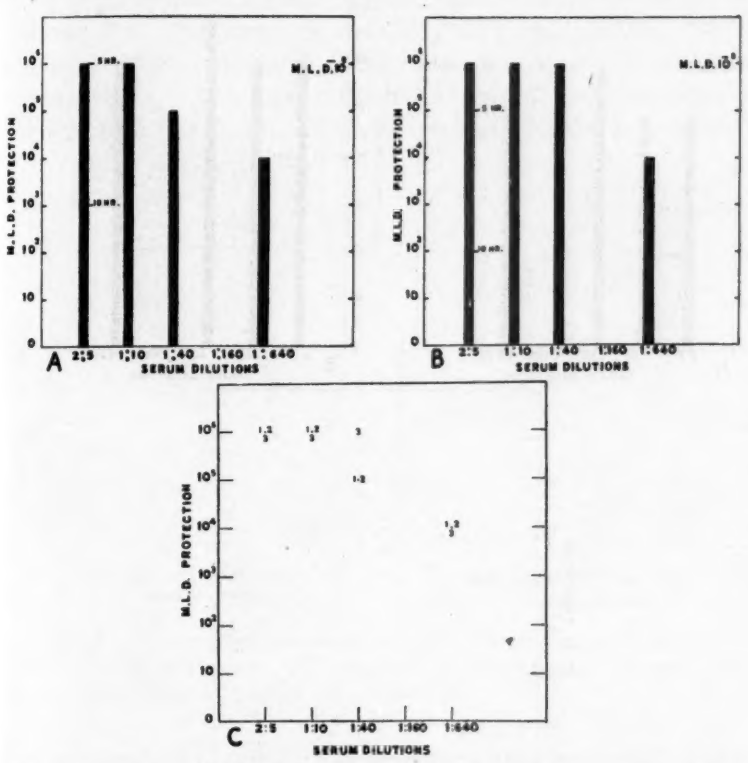

Chart 2.—*A*, protection obtained with New York state unconcentrated serum against a single strain, from a patient who recovered. *B*, protection obtained with New York state unconcentrated serum against a second single strain from a patient who recovered. *C*, composite representation of 3 protection tests using New York state unconcentrated serum against 3 different strains.

organisms. On the 2:5 column is recorded the number of minimal lethal doses against which protection was obtained when this dilution was given five and ten hours after the organisms.

A separate composite representation of each of the 3 serums demonstrates the protection obtained against all strains on which each was tested (charts 1 *C*, 2 *C* and 3 *C*).

RESULTS

When the results of 10 tests using 10 different strains treated by unconcentrated commercial serum are superimposed, in chart 1 *C*, it is seen that the protective values lie close to the same general curve, which falls with increase in the dilution of serum. All points representing protection against a single strain with dilutions of the serum

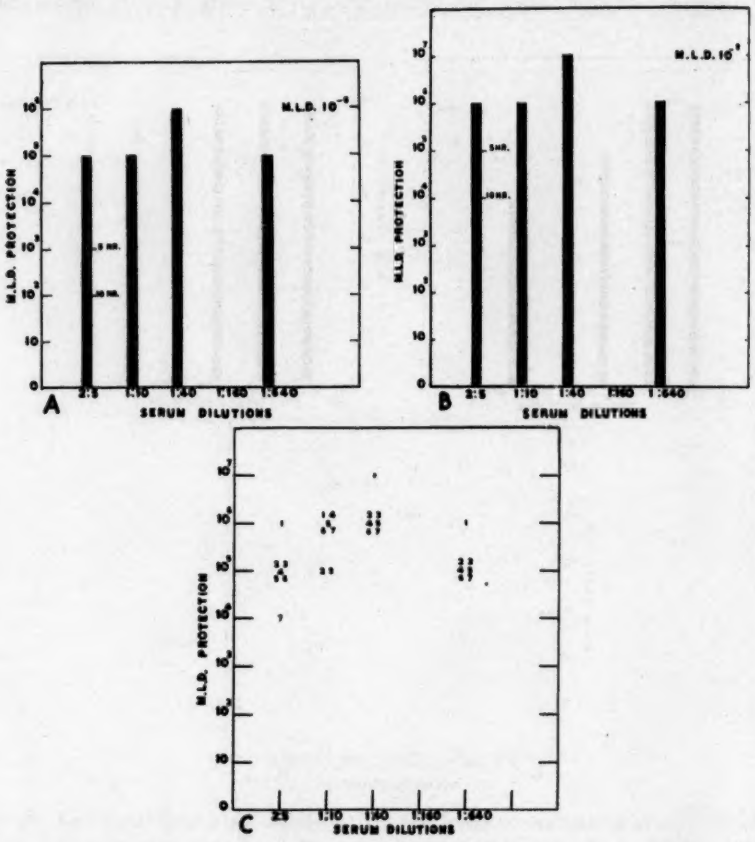

Chart 3.—*A*, protection obtained with New York state concentrated serum against a single strain from a patient who recovered. *B*, protection obtained with New York state concentrated serum against a second single strain from a patient who recovered. *C*, composite representation of 7 protection tests using New York state concentrated serum against 7 different strains.

used are indicated by the same number, so that the protection curve of each of the 10 strains can be followed. The numbers therefore range from 1 to 10. All the figures grouped about a point represent identical values.

The composite representation, in chart 2 *C*, of results of 3 protection tests with New York state unconcentrated serum, demonstrates parallel protection against 3 different strains. The curve is similar to that obtained with the unconcentrated commercial serum, the majority of tests showing protection against 1,000,000 minimal lethal doses with the 2:5 dilution and against 10,000 minimal lethal doses with the 1:640 dilution.

It is interesting that the 2:5 dilution of New York state concentrated serum fails to protect as well as the 1:40 dilution and that the value of the 1:640 dilution is equal to that of the 2:5 dilution (chart 3 *A* and *B*). The range of variability of protection with this serum against 7 different strains is rather small, as is shown in the composite representation 3 *C*. The difference between the composite curve obtained with this serum and those obtained with the 2 unconcentrated

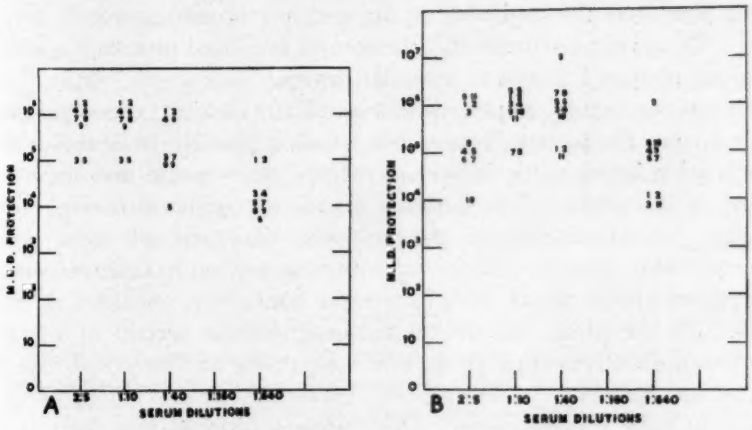

Chart 4.—*A*, composite representation of 9 protection tests against strains from 9 patients who died. *B*, composite representation of 11 protection tests against strains from 11 patients who recovered.

serums (charts 1 *C* and 2 *C*) demonstrates the consistency of the phenomenon just described. Since similar results were found in each test performed with New York concentrated serum and in none of the tests using an unconcentrated serum, this observation seems to be significant. The question arises whether or not this unfavorable effect of a larger dose of serum can be of the same nature as the severe reaction which occurs in patients with sepsis when the full dose of antiserum is given at one time. Dr. Schwentker has been able to avoid this reaction in most patients by starting with small doses of serum and increasing the dose at short intervals. Other explanations present themselves, and the problem will be pursued. Similar results were

obtained by Goodner and Horsfall [5] in mouse protection tests against pneumococci when they used horse antiserums but not when they used rabbit antiserums. They explained this prozone phenomenon on the basis of lipid composition of the serum.

Composite chart 4 compares the protective value of therapeutic serums against strains from patients who died with the protection obtained against strains from patients who apparently responded dramatically to the antiserums. It is apparent that there is no significant difference between the protection obtained against strains from those who died and that against strains from those who recovered.

SUMMARY

The mouse protection test has been examined for its reliability in providing an objective method for testing the efficacy of antimeningococcus serums at the beginning of an epidemic of meningococcic meningitis. It was demonstrated that the serums employed protected against a number of type I strains to a similar degree.

Using the serum employed therapeutically against the organism isolated from the patient, I have not found it possible to demonstrate a correlation between the individual therapeutic response and the protective value in mice. The duration of infection prior to therapy and the age distribution of the patients who died and of those who recovered were similar. Of the patients who died, only those who had received treatment for at least forty-eight hours were included in this study. On the whole, the clinical response to these serums in a large series was good, resulting in as low a mortality as one could expect during an epidemic. Likewise the protection against 20 different strains in mice was excellent. The evidence suggests that there is a broad correlation between mouse protection and therapeutic value and that failure of a patient to respond to a serum which gives excellent specific protection in mice must be due to variation in the individual patient's ability to respond rather than to lack of specificity of the serum.

Dr. Huntington Williams, Dr. Myron Tull and Dr. Francis F. Schwentker, of the Baltimore Department of Health, provided the opportunity of studying the epidemic. Dr. J. Howard Brown furnished guidance in the method of culture preservation, and Dr. Geoffrey Rake gave training in the method of testing.

5. Goodner, K., and Horsfall, F. L., Jr.: J. Exper. Med. **64**:369 and 377, 1936.

EFFECT OF IRRADIATED MILKS ON STORAGE OF NITROGEN AND ACID-BASE MINERALS IN CHILDREN

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DETROIT

In the investigation reported here observations were made on the mineral storage of 8 well children 5 to 8 years of age during test periods of twenty to sixty days under closely controlled conditions of diet and environment. Each child studied received first nonirradiated milk and later irradiated milk of the same kind and quantity. Three of the children were given fluid milk, 3 were given evaporated milk and 2 were given a combination of the two kinds.

METHODS

One of the greatest burdens in a continuous study with such a rigid regimen is the maintenance of the morale of the subjects. The Methodist Children's Village afforded ideal facilities for metabolic observations. At the village 8 to 10 children live together in a home unit with a house mother; this arrangement kept the study group together without disrupting the routine of the happy, healthy children. The experimental subjects went to school and to Sunday school in the village; they enjoyed their customary freedom of play out of doors with pets and playthings; they were given every opportunity for unhampered social and physical development. They slept in individual beds and in pleasant airy rooms. The children were at all times, even when going to and from school, under the continuous observation of a trained person, so it is known that no metabolic samples were lost or extra foods eaten because of prank or forgetfulness. During the investigation two mature women with experience in handling children were employed to direct the daily routine of living (sleeping, dressing, bathing, eating) and to preserve happiness and serenity among the children.

The tentative selection of the 8 children (4 boys and 4 girls) was based on the following criteria: a minimum of previous illness in the medical history;

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From the Research Laboratory, Children's Fund of Michigan, in cooperation with the Methodist Children's Village.

approximately average stature and weight for age; good appetite with no known idiosyncrasies; acceptable skeletal structure and development, and a disposition amenable to control by several persons over a period of months. The final selection was made from the ratings of a series of roentgenograms [1] taken three months before and again at the beginning of the metabolic collections. The subjects selected for the experiment had approximately average height, weight and general development.[2] In an attempt to standardize their nutritive state and thereby the mineral storages and subsequent mineral retaining power, the children were given a minimum of 1 quart (946 cc.) of milk daily for three months prior to the initiation of the metabolic regime.

Fourteen anthropometric measurements were made monthly by a physician [3] in the usual environment of the clinic at the Children's Village; these included circumference of head, chest, abdomen, upper part of arm and thigh, determined with the steel metric tape with constant tension Gülick spring handle; biacromial, biiliac and bitrochanteric diameter and tibial length, determined with the anthropometer. Every fifth day, horizontal total body length and stem length were determined on the measuring board when the subject arose in the morning, and the nude subjects were weighed before breakfast, after urination and, when possible, after evacuation of the bowel, in order that the measurements for all children and successive measurements for each child might be kept as consistent as possible. The Tröemmer beam balance used weighs accurately to within a range of 2 Gm.

The basal diet, which was consistent with accepted medical and dietetic practice, utilized twenty-one common foods [4] which are inexpensive and available at all seasons of the year. Similar quantities of each food were given to each child according to his age and activity, identical amounts being given the same child throughout each test period. Staple foods were purchased in the largest possible quantities practical at one time, in order that inherent variations in composition might be minimized. In this investigaton, which extended over six months, it was necessary to purchase fresh fruits, vegetables and meat from consistent sources and standard types of breads from one bakery. Bananas of constant ripeness, selected by experienced wholesalers, were delivered from the warehouse twice weekly, in order that they might approximate the state of full maturity when consumed, i. e., with fairly constant distribution of available carbohydrate.

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1. The late T. Wingate Todd, M.D., and C. C. Francis, M.D., Western Reserve University, evaluated and studied the skeletal maturity of all the children considered, particularly those finally chosen for the metabolic study.

2. Meredith, H. V.: The Rhythm of Physical Growth: A Study of Eighteen Anthropometric Measurements on Iowa City White Males Ranging in Age Between Birth and Eighteen Years, Studies in Child Welfare, Iowa City, University of Iowa, 1935, vol. 11, no. 3. Boynton, B.: The Physical Growth of Girls: A Study of the Rhythm of Physical Growth from Anthropometric Measurements on Girls Between Birth and Eighteen Years, ibid., 1936, vol. 12, no. 4.

3. Marsh W. Poole, M.D., attending physician at the Methodist Children's Village, made the medical examinations and physical measurements and cared for the children's health.

4. The basal diet was composed of apple, banana, beef, white and whole wheat bread, butter, cabbage, carrots, cheese, eggs, graham crackers, lettuce, milk, peanut butter, potato, shredded wheat or corn flakes, tomato and orange juice, sugar and salt.

The total daily allotments of food were weighed separately for each child. The raw foods were prepared in combinations and cooked in separate pottery or porcelain dishes for individual servings. Duplicates of the complete daily diet were weighed and prepared in the same manner for chemical analysis.

Because of the difficulty in obtaining a constant quantity and quality of particular foods for each child from day to day, specific manipulations were necessary. For instance, owing to the variability in the size of eggs, the number needed for the day's supply were thoroughly mixed, either uncooked or after cooking in the shell, which made it possible to weigh a 50 Gm. homogeneous portion. Butter may contain varying quantities of protein and minerals; therefore, butter fat was prepared by heating and washing sweet butter with distilled water and filtering off the fat. Both sugar and distilled water used for cooking and drinking were permitted ad libitum, but the quantities were accurately recorded. All the milk used in the study was collected from the same group of cows, in order that a greater uniformity of composition [5] might be assured. All of the nonirradiated and irradiated fluid milk, derived from the same source and subjected to the same standard methods of collection, handling and preparation, was held in refrigeration in quantities ample for each five day balance period. Large quantities of evaporated milk were prepared from the nonirradiated and the irradiated fluid milk from an identical source under specially supervised conditions, so that both the plain and the irradiated evaporated milk were consistent in chemical content. These procedures assured a milk supply of unvarying quality throughout each balance period.[6] The initial age, the initial date of study, the length of the periods for nonirradiated and irradiated milk and the amount and kind of milk ingested are given for each child in table 1.

Frequent periodic assays were made of the vitamin D content of the milk.[7] Both the fluid and the evaporated milk were assayed. The irradiated fluid milk was tested ten times between October 1935 and April 1936. The average potency per quart was 235 U. S. P. units, with a range from 215 to 270 units. The irradiated evaporated milk (prepared from one batch of raw milk) contained 203 units per 14½ ounce (383 Gm.) can.

The vitamin D supplements obtained from the irradiated milk amounted to 96 U. S. P. units daily for the children who changed from plain to irradiated fluid milk, 90 U. S. P. units for those who changed from plain to irradiated evaporated milk (diluted 1 : 1 with water) and 182 U. S. P. units for the 2 boys receiving both fluid and evaporated milk, plain and irradiated.

In order that the children might not tire of this rigidly controlled diet, great care and ingenuity were used in the planning of the menus. The children were

5. The average composition of milk, in grams per hundred grams (irradiated and nonirradiated milk had the same average chemical composition) was as follows:

Milk	Nitrogen	Calcium	Magnesium	Sodium	Potassium	Phosphorus	Chlorine	Sulfur	Iron	Fat
Fluid	0.492	0.118	0.012	0.048	0.148	0.089	0.108	0.027	0.00004	3.10
Evaporated.	0.508	0.130	0.013	0.071	0.151	0.108	0.106	0.035	0.00006	3.92

6. Mr. C. G. Reichle, plant manager of the Detroit Branch of the Borden Farm Products Company of Michigan, controlled the handling of all the milk used in this study.

7. The vitamin D tests were made at periodic intervals by the Wisconsin Alumni Research Foundation under the supervision of Henry T. Scott, Ph.D., and independently by C. A. Hoppert, Ph.D., Michigan State College, East Lansing, Mich.

content with their food and frequently expressed verbal approval concerning their enjoyment of meals. Three women, all trained in nutrition and dietetics, took charge of constructing the menus, weighing and preparing all food and fluids for consumption, assisting the house mother in the supervision of the children during mealtime and collecting the metabolic specimens of food, urine and feces. In addition, these trained workers determined the basal metabolic rates of the children at stated intervals and recorded the body weights, recumbent total and stem lengths, emotional behavior, intensity of activity and many other pertinent facts.

Complete cooperation and understanding on the part of the children were necessary for complete consumption of all food given and for accurate collection of the urine and feces in separate jars. The urine was pooled in 1 sample for twenty-four hours, preserved with toluene and refrigerated. The twenty-four hour samples of urine were raised in volume to the nearest multiple of 100 cc., and one fifth of this quantity was pooled for the representative five day composite specimen used for determining the metabolic balance. In order to mark off the feces, 0.2 to 0.3 Gm. of carmine was given before breakfast on the first day of each successive balance period. The stools were evacuated into individual weighed glass jars with covers, labeled with the name of the child and the time of defecation and refrigerated until daily delivery to the laboratory.

The individual wet stools for each child were weighed daily, transferred quantitatively with distilled water into a special glass container and kept at a low temperature until the collection for the five day metabolic balance period was completed. The pooled specimens in the jar were then thoroughly mixed with a mechanical stirrer until a homogeneous mixture resulted. One portion, by weight, was dried with alcohol; this served as the sample for which sulfur, phosphorus and chlorine were determined.[8] An equal portion was hydrolyzed with 200 cc. of concentrated hydrochloric acid at approximately 100 C. until the suspension could be homogenized, raised to a standard volume and quantitatively pipetted for the analysis of nitrogen, calcium, magnesium, sodium and potassium.[8] The duplicate diets were treated in the same manner as the feces.[8] While some data are available concerning the mineral balances of infants and of adults, little work has been reported on the base balances of children. When data on all the acid-forming and base-forming elements are available, many pertinent observations are made possible which would not be apparent from calcium, phosphorus and nitrogen balances alone.

This paper considers only the influence of irradiated fluid and irradiated evaporated milk on the storage of nitrogen and of the acid-base minerals of 8 children. (A previous report presented the comparison of fluid and evaporated milk.[9])

RESULTS AND COMMENT

With each child serving as his own control, in order that each subject might have the same nutritive background and identical hereditary influences under which to test the effect of irradiated milk, an opportunity was provided for studying variability in the same child and variations in response among the different subjects. To avoid any cumulative effect

8. Detailed descriptions of the methods and chemical procedures will be presented in a forthcoming monograph.

9. Hunscher, H. A.; Hummel, F. C., and Macy, I. G.: The Influence of Fluid and Evaporated Milks on the Storage of Nitrogen and Acid-Base Minerals in Children, Am. J. Dis. Child. **58**:529 (Sept.) 1939.

of vitamin D, the periods of intake of irradiated milk followed those of nonirradiated milk in all cases. The 3 children who were observed in the late fall showed no results which could be ascribed to a cumulative effect of vitamin D derived from the summer sunshine when compared with the 5 who were studied during the darker winter months. For all the children, however, any effect of sunshine would have been greater during the earlier period, when nonirradiated milk was given, and would have been offset by the vitamin D supplement during the period when irradiated milk was given; this would tend to minimize the observed effect of the vitamin supplement.

Table 1 shows the average daily intake and retention of nitrogen and acid-base mineral elements per kilogram of body weight for the 8 children during the periods in which the only dietary change was a substitution of an equal quantity of irradiated for nonirradiated milk. In no case (with a total of four hundred and seventy-five experimental days, two hundred and seventy with nonirradiated and two hundred and five with irradiated milk) did all of the children show any one similar physiologic tendency while taking irradiated milk. In many instances the changes in the average daily storage were so small that they preclude any estimation of possible effects of irradiation; in others, the changes, represented by the differences between averages were large but showed no definite comparative trends for the group. These results have significance, since the test periods for each subject extended over twenty to sixty consecutive days, which minimized the chances for error due to intestinal lag, separation of the feces and physiologic adjustment.

All the children showed a positive retention of the basic elements (calcium, magnesium, sodium and potassium), whether nonirradiated or irradiated milk was ingested. Likewise (table 1) the acidic elements (phosphorus, sulfur and chlorine) were stored continuously by all the children, with the exception of P. W. and J. M., who lost sulfur both with irradiated and with nonirradiated milk, and one of whom, J. M., lost phosphorus during the ingestion of nonirradiated milk. From the differences in the average daily storage per unit of body weight, it is further evident that although several of the children retained less base than acid when nonirradiated milks were given, all children had a positive base balance while taking irradiated milk. Since the skeleton contains approximately 91 per cent of the total base in the body, excess storage of base (over acid) indicates that the skeleton was developing more rapidly when irradiated milk was consumed.

While taking irradiated milk the 6 youngest children, who received a moderate amount of calcium (0.72 to 0.80 Gm. daily), showed increased storage of calcium and a more regular retention of this element, results which did not differ from those of the 2 older children, who received larger amounts (1.26 Gm. daily); in fact, the latter were

TABLE 1.—*Average Daily Intake and Retention of Children Given Nonirradiated and Irradiated Milk*

Child	Type of Milk	Length of Study,* Days	Initial Age, Mo./Days	Caloric Intake, per Kg.	Nitrogen, Mg./Kg.		Calcium, Mg./kg.		Magnesium, Mg./kg.		Sodium, Mg./Kg		Potassium, Mg./kg.		Phosphorus, Mg./Kg.		Sulfur, Mg./Kg.		Chlorine, Mg./Kg.		Fat, Gm./Kg.	
					Intake	Retention	Intake	Retention	Intake	Retention	Intake	Retention	Intake	Retention	Intake	Retention	Intake	Retention	Intake	Retention	Intake	Retention
	400 Gm. fluid milk																					
J. M.	Nonirradiated	30	73/ 4	83.0	484.6	12.2	37.0	2.6	13.7	1.2	96.2	4.9	115.5	3.3	51.0	—0.5	31.4	—1.0	155.4	13.6	2.95	2.87
	Irradiated	30	74/ 3	81.5	478.2	1.1	36.6	1.8	12.6	0.6	95.0	5.9	114.0	5.9	50.4	4.9	31.0	—0.9	153.4	9.0	3.02	2.96
B. F.	Nonirradiated	35	67/ 8	90.0	524.4	21.6	40.0	6.3	13.8	1.5	104.1	5.7	125.0	7.1	55.2	4.4	34.0	0.5	168.2	14.9	3.19	3.08
	Irradiated	30	68/12	89.1	522.2	16.4	39.9	7.4	13.7	1.2	103.7	6.5	124.5	9.9	55.0	8.0	33.8	0.5	167.5	11.3	3.30	3.20
P. W.	Nonirradiated	35	75/29	80.7	468.5	—7.8	35.8	2.4	12.3	2.2	98.0	3.2	111.6	6.9	49.4	1.9	30.4	—1.5	150.2	10.5	2.85	2.77
	Irradiated	20	77/ 3	79.5	466.4	—4.0	35.6	2.5	12.2	1.8	92.6	2.2	111.1	7.7	49.1	4.5	30.2	—0.6	149.6	6.0	2.95	2.88
	400 Gm. evaporated milk †																					
R. S.	Nonirradiated	20	69/ 0	98.6	520.4	29.8	41.4	5.3	15.1	1.2	110.8	4.2	142.7	11.8	57.7	5.6	36.0	2.7	175.3	10.4	3.94	3.82
	Irradiated	25	69/24	97.7	515.9	34.9	41.0	5.1	15.0	1.5	109.8	7.0	141.4	18.9	57.2	4.1	35.7	2.9	173.8	18.2	3.90	3.76
B. M.	Nonirradiated	25	66/15	94.7	532.4	51.6	44.0	10.3	15.3	1.4	106.3	3.6	150.8	11.3	58.5	9.7	35.9	3.1	166.6	8.2	3.66	3.57
	Irradiated	25	67/ 9	91.8	513.4	33.4	42.5	9.6	14.7	1.4	102.5	4.2	145.4	15.2	56.4	3.9	34.7	1.4	160.6	14.2	3.53	3.42
J. H.	Nonirradiated	25	59/ 0	105.7	556.2	47.3	44.2	5.6	16.1	1.6	118.4	7.6	152.5	11.0	61.7	7.3	38.5	3.4	187.4	17.0	4.21	4.12
	Irradiated	25	59/24	102.8	543.9	45.1	43.2	9.5	15.8	1.9	115.8	8.9	149.2	16.3	60.3	5.7	37.7	2.4	183.2	21.0	4.12	4.03
	400 Gm. fluid milk and 400 Gm. evaporated milk †																					
D. P.	Nonirradiated	40	100/24	82.0	441.6	14.6	45.3	5.7	11.3	2.6	87.9	9.4	108.4	8.5	53.4	11.0	29.6	1.4	137.6	16.0	3.58	3.48
	Irradiated	25	102/ 3	82.0	440.6	5.4	45.2	6.4	11.3	3.4	87.7	6.9	108.1	4.9	53.2	7.2	29.6	0.6	137.2	10.1	3.57	3.48
W. P.	Nonirradiated	60	97/14	95.4	513.8	36.3	52.7	4.2	13.2	0.8	102.3	3.7	126.1	11.1	63.1	9.3	34.5	2.0	160.1	8.8	4.16	4.03
	Irradiated	25	99/17	92.9	497.2	33.5	51.0	6.0	12.8	1.2	99.0	4.8	122.0	12.4	60.1	5.4	33.3	1.4	154.9	8.7	4.03	3.88
M ± SEM‡	Nonirradiated				501.5± 4.8	24.8± 3.3	43.6± 0.8	5.1± 0.5	13.4± 0.2	1.6± 0.1	101.0± 1.2	5.2± 0.8	126.2± 2.1	8.8± 0.7	56.3± 0.7	6.4± 0.7	33.4± 0.4	1.2± 0.3	160.3± 1.8	12.2± 1.1		
	Irradiated				498.1± 5.0	20.7± 3.3	41.8± 0.7	6.0± 0.7	13.5± 0.2	1.6± 0.2	100.9± 1.3	5.9± 0.6	127.0± 2.3	11.3± 1.2	55.2± 0.7	5.5± 0.5	33.3± 1.1	0.9± 0.3	160.1± 2.2	12.3± 3.0		

* Five day balance periods.
† 200 Gm. of evaporated milk diluted 1:1 with water.
‡ Mean plus or minus standard error of mean.

less efficient in the utilization of their double intakes of calcium, whether derived from nonirradiated or from irradiated milk (table 2).

It is not surprising that the increased intake of vitamin D in the form of irradiated milk (90 to 95 U. S. P. units daily for 6 children and 180 to 190 units for the other 2) did not cause a significantly greater storage of minerals, as judged by the average daily retention. These well children were selected because of their previous good health and development and lived in the open country, where they played in the sunshine; moreover, they consumed some vitamin D in a general mixed dietary which furnished daily, per kilogram of body weight, 440 to 556 mg. of nitrogen, 79 to 106 calories, 35 to 53 mg. of calcium and 49 to 62 mg. of phosphorus. In addition, the bodily stores of calcium and phosphorus were undoubtedly well filled from the three month period of prefeeding in the summer. In other words, there is every reason to believe that the subjects' pre-existing nutritive state and dietary were good [10] and that the degree of calcium saturation in their skeletal tissues was uniform; therefore, the efficiency of their calcium utilization was not affected by depletion or replenishment of stores or by a chronically subnormal nutritional state.[11] This is in accord with Orr's statement: [12] "The most that can be done by diet or other environmental factors is to enable the individual to attain his full inherited capacity for growth and health."

These various contentions are sustained in this study by the results obtained with W. P. This was the only subject who did not receive the supervised, three month preliminary feeding, although he was reported to have received between a pint and a quart of milk daily and was 1 of the 2 children who received the higher intake of calcium and vitamin D; yet his results were comparable to those of the other children. In the same child, there was not indicated by the average daily retention of any of the elements a consistent enhanced storage which could be attributed to the vitamin D derived from the irradiated milk.

In this group of children (table 1) the means of the daily retentions of calcium per kilogram of body weight varied between 2 and 10 mg., regardless of whether additional vitamin D in the form of irradiated milk was in the diet. The average daily calcium retention for the entire

10. Clark, G. W.: Studies in the Mineral Metabolism of Adult Man, Univ California Publ., Physiol. **5**:195, 1926.

11. Fairbanks, B. W., and Mitchell, H. H.: The Relation Between Calcium Retention and the Store of Calcium in the Body, with Particular Reference to the Determination of Calcium Requirements, J. Nutrition **11**:551, 1936. Rottensten, K. V.: The Effect of Body Stores on the Efficiency of Calcium Utilization, Biochem. J. **32**:1285, 1938.

12. Orr, J. B.: Food, Health and Income: Report on a Survey of Adequacy of Diet in Relation to Income, New York, The Macmillan Company, 1936.

group was 5.65 mg. per kilogram during both periods of study (with nonirradiated milk, 5.1; with irradiated, 6.0). This value for healthy and highly standardized children [13] is less than the values postulated as desirable by Sherman and Hawley [14] and markedly lower than those calculated by Leitch,[15] who did not take into consideration the previous nutritional state in regard to calcium of the subjects from whom she chose her data. Because of their nutritional stability this group of children did not need so large a retention of the mineral to satisfy the fluctuating requirements of the growth impulse.

The addition by irradiated milk of 90 to 95 U. S. P. units of vitamin D to the diet of each of the 6 youngest children, who had a lower calcium intake, and of 180 to 190 U. S. P. units to the diet of each of the older ones, who had the higher mineral intake, seemed to produce a more regular effect on the calcium retentions, as shown in the chart. A decrease in the calcium retention of P. W. for two periods coincided with an attack of bronchitis. The value obtained during the following period apparently portrays an acceleration in retention of calcium to compensate for the loss during suboptimal health. During the first two periods of ingestion of irradiated milk J. M. showed first a considerable decrease in retention of calcium and then a closely corresponding increase. Soft and unformed stools are difficult to separate accurately, and during the first period this child had stools the wet weight of which was, roughly, 20 per cent greater than that of the second period; this indicates that an excess of fecal material was included for the second period. This interpretation is strengthened by the constancy of the urinary determinations, which showed no compatible change in mineral content.

This study concerning the influence of additional supplements of vitamin D in the form of irradiated milk on the acid-base mineral and nitrogen metabolism of children was carried out over a sufficiently long time to offer an opportunity of studying the interaction of the various components of bone and soft tissue (calcium-phosphorus, nitrogen-phosphorus) in the metabolism of growth. Table 2 indicates the maximum and minimum daily retention of nitrogen, calcium and phosphorus, together with the percentages of the intakes of these elements retained by the individual children while they were receiving a diet changed only by the addition of vitamin D. In the case of calcium it may be seen that 4

13. Erickson, B. N.; Williams, H. H.; Hummel, F. C., and Macy, I. G.: The Lipid and Mineral Distribution in the Serum and Erythrocytes of Normal Children, J. Biol. Chem. **118**:15, 1937.

14. Sherman, H. C., and Hawley, E.: Calcium and Phosphorus Metabolism in Childhood, J. Biol. Chem. **53**:375, 1922.

15. Leitch, I.: The Determination of the Calcium Requirements of Man, Nutrition Abstr. & Rev. **6**:553, 1937.

of the subjects (B. F., and J. H., D. P., W. P.) responded with a more efficient utilization when additional vitamin D was given, while the remaining 4 (P. W., J. M., R. S., B. M.) showed decreased utilization. The percentage of phosphorus intake retained gave an inverse relationship to that of calcium for 5 of the 8 children during the intake of irradiated

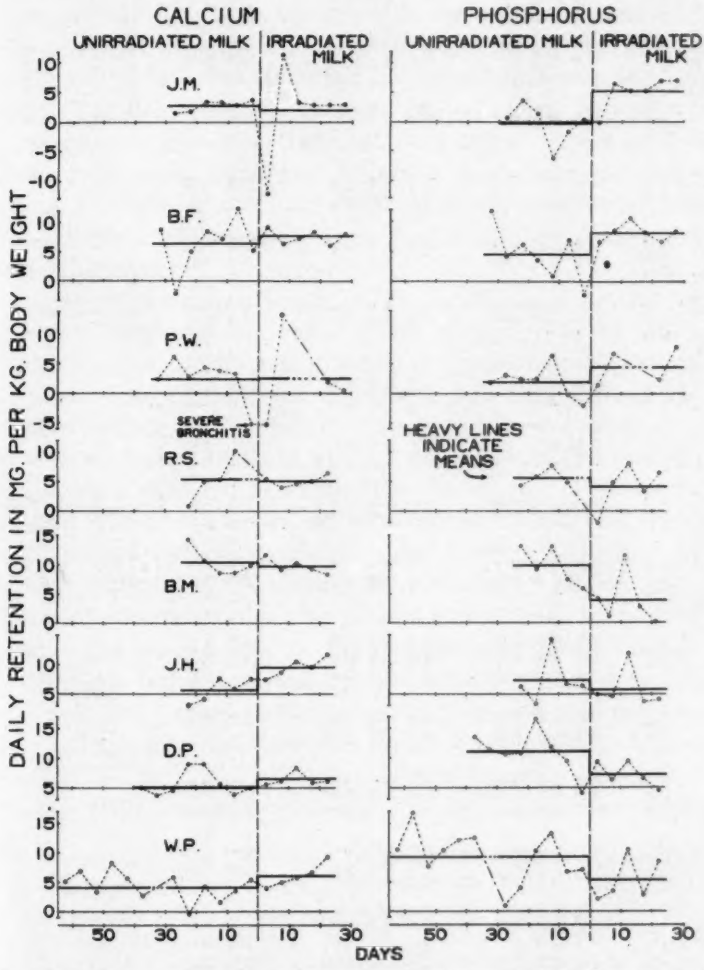

Chart illustrating differences in retention of calcium and of phosphorus during ingestion of irradiated and of nonirradiated milk.

milk; i. e., if the percentage of calcium retention increased, the percentage of phosphorus utilization decreased. It is generally accepted that the ratio of calcium to phosphorus (grams) in the bone is 2: 1, and over 98 per cent of the calcium retained goes into building bone. On the

TABLE 2.—*Range and Percentage of Retention of Nitrogen, Calcium and Phosphorus During the Consumption of Nonirradiated and Irradiated Milk*

Child	Type of Milk	Length of Study,* Days	Initial Date of Study	Height		Weight		Nitrogen				Calcium			Phosphorus‖			Calcium-Phosphorus Ratio		Base Minus Acid, mEq./Kg./24 Hr.	
								Retention, Mg./Kg./24 Hr.		R/I,§	R/A,§	Retention, Mg./Kg./24 Hr.		R/I,§	Retention, Mg./Kg./24 Hr.		R/1,§				
				Initial, Cm.	Daily Gain, Cm.	Initial, Kg.	Daily Gain, Kg.	Minimum	Maximum	Percentage	Percentage	Minimum	Maximum	Percentage	Minimum	Maximum	Percentage	Intake	Retention	Intake	Retention
	400 Gm. fluid milk																				
J. M.	Nonirradiated	30	10/ 5/35	115.4	0.010	19.37	0.0087	— 4.6	26.2	2.54	2.83	1.3	3.4	6.95	—6.5	3.4	....	0.72	....	0.72	0.23
	Irradiated	30	11/ 4/35	115.7	0.017	19.63	0.0150	—23.4	9.6	0.21	0.24	—12.2	11.3	4.82	—0.4	6.7	9.69	0.72	0.37	0.72	0.07
B. F.	Nonirradiated	35	9/30/35	108.2	0.023	18.07	0.0008	3.3	47.1	4.13	4.64	— 2.2	12.2	15.81	—2.4	11.6	7.96	0.72	1.43	0.78	0.16
	Irradiated	30	11/ 4/35	109.0	0.033	18.10	0.0023	— 7.2	31.5	3.17	3.51	5.9	8.9	18.47	6.4	10.4	14.51	0.72	0.92	0.78	0.20
P. W.	Nonirradiated	35	9/30/35	116.0	0.026	20.52	—0.0108	—18.2	7.4	....	....	— 5.3	6.1	6.86	—2.1	6.3	3.92	0.72	1.26	0.70	0.31
	Irradiated	20	11/ 4/35	116.9	0.033	20.14	0.0137	—17.4	4.0	....	....	— 5.4	13.2	4.89	1.4	7.7	5.69	0.72	0.56	0.70	0.17
	400 Gm. evaporated milk †																				
R. S.	Nonirradiated	20	1/13/36	115.9	0.015	19.30	0.0090	— 1.5	55.4	5.73	6.50	0.7	10.2	12.81	4.3	7.7	9.78	0.72	0.95	1.23	0.06
	Irradiated	25	2/ 7/36	116.3	0.028	19.50	0.0088	14.4	50.7	6.72	7.69	4.0	6.4	12.46	—2.2	8.1	7.20	0.72	1.24	1.22	0.24
B. M.	Nonirradiated	25	1/13/36	106.7	0.012	17.27	0.0240	31.6	99.0	9.66	10.69	8.5	14.1	23.37	5.9	13.1	16.62	0.75	1.06	1.60	0.59
	Irradiated	25	2/ 7/36	107.0	0.032	17.37	0.0208	23.4	53.9	6.54	7.30	8.2	11.5	22.46	0.1	11.4	6.87	0.75	2.46	1.54	0.44
J. H.	Nonirradiated	25	1/13/36	108.2	0.016	17.92	0.0232	26.5	58.2	8.50	9.54	3.0	7.6	12.61	3.2	14.2	11.85	0.72	0.77	1.32	—0.10
	Irradiated	25	2/ 7/36	108.6	0.024	18.50	0.0088	17.1	64.2	8.30	9.38	7.3	11.6	22.09	3.6	11.7	9.45	0.72	1.67	1.29	0.35
	400 Gm. fluid milk and 400 Gm. evaporated milk †																				
D. P.	Nonirradiated	40	12/ 4/35	137.6	0.022	27.89	—0.0018	—14.5	42.0	3.34	3.68	3.6	9.0	12.57	3.9	16.5	20.52	0.85	0.52	0.96	—0.05
	Irradiated	25	1/13/36	138.5	0.004	27.82	0.0120	— 9.6	23.0	1.22	1.34	5.5	8.3	14.00	4.4	9.4	13.52	0.85	0.89	0.96	0.28
W. P.	Nonirradiated	60	12/ 4/35	119.5	0.011	23.19	0.0202	— 8.0	71.4	7.08	7.89	— 0.5	8.2	8.08	0.9	16.6	14.92	0.85	0.45	1.12	—0.18
	Irradiated	25	2/ 7/36	120.2	0.016	24.50	0.0168	24.7	45.8	6.76	7.51	3.8	9.1	11.77	1.9	10.4	8.99	0.85	1.11	1.08	0.28

SD ± SE_{SD} ‡

	Nitrogen	Calcium	Phosphorus
Nonirradiated milk			
Intake	35.6 ± 3.4	5.8 ± 0.6	5.1 ± 0.5
Retention	24.6 ± 2.4	3.4 ± 0.3	5.2 ± 0.5
Irradiated milk			
Intake	32.0 ± 3.5	4.8 ± 0.5	4.4 ± 0.5
Retention	21.4 ± 2.4	4.5 ± 0.5	3.3 ± 0.4

* Five day balance period.
† 200 Gm. of evaporated milk diluted 1:1 with water.
‡ Standard deviation plus or minus standard error of standard deviation.
‖ The valence of 1.8 was used in calculation of phosphorus (Shohl, A. T.: Mineral Metabolism in Relation to Acid-Base Equilibrium, Physiol. Rev. 3: 509, 1923).

other hand, phosphorus not only is essential for the skeleton, which claims about 70 per cent of that retained, but is an important component of the soft tissues.

The calcium-phosphorus ratio in the intake varied from 0.72 to 0.75 among the 6 smaller children and was 0.85 for the 2 older ones; the ratio in the retention, on the other hand, fluctuated from 0.37 to 2.46 (table 2). The wide variations in the calcium-phosphorus ratios in the retention demonstrate changing demands for the minerals laid down in the skeletal structure and in the soft muscular and glandular tissues. The determination of this ratio gives an indication of the relative rates of growth of bone and soft tissue. Ratios of about 1.5 indicate a relatively equal rate of formation of bone and soft tissue; ratios of less than 1 indicate a rapid synthesis of muscular, neural or glandular tissue, while ratios greater than 2 indicate a rapid deposition of osseous material.[16]

Five of the 8 children (R. S., J. H., B. M., D. P., W. P.) showed higher calcium-phosphorus ratios while taking irradiated milk, which indicates that the additional vitamin D stimulated the rate of bone deposition. Two of the other 3 children (P. W., B. F.), who were studied in the fall, showed just the reverse, while no comparison is possible with the remaining child, as there was a loss of phosphorus during the ingestion of nonirradiated milk. That the vitamin D derived from the irradiated milk had a beneficial influence on the skeletal structure is more conclusively shown by the more rapid average daily gain in length of all but 1 child (D. P.) during the intake of irradiated milk, which substantiates the observation that vitamin D intake and linear growth are related.[17] The oldest child (D. P.) had grown at a rapid rate for four years previous to this study and had attained a skeletal maturity approximately two years ahead of his chronologic age; so it is not surprising that he did not show an observable response to the daily supplement of 180 to 190 U. S. P. units of vitamin D in the irradiated milk. Moreover, this child had been receiving sufficient calcium and vitamin D

16. Stearns, G.: The Significance of the Retention Ratio of Calcium: Phosphorus in Infants and Children, Am. J. Dis. Child. **42**:749 (Oct., pt. 1) 1931. Jeans, P. C., and Stearns, G.: The Human Requirement of Vitamin D, J. A. M. A. **111**: 703 (Aug. 20) 1938.

17. Stearns, G.; Jeans, P. C., and Vandecar, V.: The Effect of Vitamin D on Linear Growth in Infancy, J. Pediat. **9**:1, 1936. Slyker, F.; Hamil, B. M.; Poole, M. W.; Cooley, T. B., and Macy, I. G.: Relationship Between Vitamin D Intake and Linear Growth in Infants, Proc. Soc. Exper. Biol. & Med. **37**:499, 1937. Jeans, P. C., and Stearns, G.: The Effect of Vitamin D on Linear Growth in Infancy: II. The Effect of Intakes Above 1,800 U. S. P. Units Daily, J. Pediat. **13**:730, 1938. Roberts, L. J.; Blair, R.; Lenning, B., and Scott, M.: Effect of Milk Supplement on Physical Status of Institutional Children: I. Growth in Height and Weight, Am. J. Dis. Child. **56**:287 (Aug.) 1938.

to keep his skeletal tissues saturated; he had been in calcium equilibrium for sixty-five days before the experimental periods, with a calcium intake of approximately 0.8 Gm. daily and no added vitamin D. With an augmented milk intake of 400 Gm. during the present study, he increased his storage of calcium, though he was less efficient in his utilization; this condition was not changed by substitution of irradiated milk containing 180 to 190 U. S. P. units of vitamin D daily for an equal quantity of nonirradiated milk.

A positive nitrogen balance (excess of intake over outgo) involves bodily storage of protein, which becomes an integral part of the soft tissues, particularly the muscles, the parenchymatous organs and the nerves. Thus the retention of nitrogen is a more exact measure of growth than increase in weight, which may be due in a varying degree to body water and fat (table 1). As nitrogen is deposited it carries with it the major portion of the stored sulfur and 30 to 40 per cent of the retained phosphorus. The percentage of nitrogen intake retained varied from 9.66 to 2.54 during intake of nonirradiated milk and from 8.30 to 0.21 during intake of irradiated milk. In 1 case (P. W.) a continuous loss of nitrogen was paralleled throughout the study by a loss of sulfur, which was greater during the intake of nonirradiated milk. Although P. W. gained in weight while ingesting irradiated milk, the increase was due to shifting of water or fattening and not to growth of muscle tissue. All subjects, with the exception of R. S., showed decreased utilization of nitrogen while receiving irradiated milk. In this study, in which the test periods extended twenty to sixty days, there was a consistent relation between the percentage of nitrogen retained and the percentage utilized,[18] in accordance with the observation of Gordon and associates.[19] Four of the 5 children who built skeletal tissue at a more rapid rate during the ingestion of irradiated milk had a lowered retention of nitrogen (J. H., B. M., D. P., W. P.). This is further evidence that the soft tissues were developing at a slower rate during ingestion of irradiated milk and that the additional vitamin D stimulated formation of bone.

The relation between the metabolism of nitrogen and that of sulfur is further illustrated in table 1. In this study the sulfur retentions of 7 children follow the same trend as the nitrogen retentions; an increased retention of nitrogen is paralleled by increased retention of sulfur, or

18. The ratio of nitrogen retained to nitrogen apparently absorbed, i. e., $\frac{\text{dietary N} - (\text{fecal N} + \text{urinary N})}{\text{dietary N} - \text{fecal N}} \times 100$, is called the percentage of utilization.

19. Gordon, H. H.; Levine, S. Z.; Wheatley, M. A., and Marples, E.: Respiratory Metabolism in Infancy and in Childhood: XX. The Nitrogen Metabolism in Premature Infants—Comparative Studies of Human Milk and Cow's Milk, Am. J. Dis. Child. **54**:1030 (Nov.) 1937.

vice versa. The correlation between the 117 paired determinations of these elements is found to be $r_{SN} = 0.73 \pm 0.06$. The relation between sulfur and nitrogen can be shown to be linear, as expressed by the equation S = 4.57 N—0.61, S and N denoting, respectively, sulfur and nitrogen. The standard error of prediction is 1.37.

In order to test the data further, to ascertain whether the retentions of nitrogen and the seven acid-base minerals were significantly different during the intake of irradiated milk from the retentions during the intake of nonirradiated milk, the analysis of variance [20] was applied (table 3).

Variation may be due to factors other than the change from nonirradiated to irradiated milk: Some of the children were receiving

TABLE 3.—*Analysis of Variance of Nitrogen, Phosphorus and Sulfur Retentions*

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square Variation	F	F for 1% Significance
Nitrogen:					
Between nonirradiated and irradiated milk	1	0.5180	0.5180	16.656	6.92
Between fluid and evaporated milk	2	8.4313			
Between individuals	7	12.8684			
Experimental error	86	2.6715			
Total	96	24.4892			
Phosphorus:					
Between nonirradiated and irradiated milk	1	95.4394	95.4394	16.8398	6.92
Between fluid and evaporated milk	2	1461.2127			
Between individuals	7	1714.0288			
Experimental error	86	487.4057			
Total	96	3758.0866			
Sulfur:					
Between nonirradiated and irradiated milk	1	21.8674	21.8674	14.5260	6.92
Between fluid and evaporated milk	2	358.1335			
Between individuals	7	447.5895			
Experimental error	86	129.4694			
Total	96	957.0598			

evaporated milk, while others were given fluid milk; 8 children were included in this study, and this factor alone might have been an important source of variation. Table 3 lists the sum of the squares for each of these sources of variation, together with their respective number of degrees of freedom, always 1 less than the number in the groups: For example, there are 8 children, so the number of degrees of freedom is 7. The variation that is not accounted for by any of the factors mentioned we have termed experimental error. *F* is a ratio [20] which for this particular problem would not be expected to exceed 6.92 more than once in a hundred trials in chance distributions. Of the eight ele-

20. Snedecor, G. W.: Calculation and Interpretation of Analysis of Variance and Covariance, Ames, Iowa, Collegiate Press, Inc., 1934. Tippett, L. H. C.: The Methods of Statistics: An Introduction for Workers in the Biological Sciences, London, Williams & Norgate, Ltd., 1931.

ments, nitrogen, phosphorus and sulfur were the only ones for which the average daily retention was significantly different during ingestion of the two types of milk. For these elements the ratio F is more than twice 6.92, indicating that the differences in the means of the retentions of these elements during intake of the different types of milk is highly significant. This significant decrease in retention of nitrogen, phosphorus and sulfur during ingestion of irradiated milk supports other indications of a shift in type of tissue formed as a result of the vitamin D supplement, from soft tissue with nonirradiated milk to skeletal tissue with irradiated milk. A study of the fat utilization and fecal lipid partition of the children failed to reveal any influence due to the irradiated milk, as illustrated by the data presented in table 2.

The periods of observation were too short for one to ascertain the influence of the irradiated milk on the dental structures of the children. However, it is interesting that although neither tooth paste nor dental cleansing agents could be used during the eight months of the metabolic study (since they would have introduced unmeasurable foreign material into the mouths), the mouths of the children remained exceptionally clean and an improvement in the nutritional state of both the gums and the teeth was observed during frequent detailed examinations by a dentist experienced with children.[21] These beneficial results, however, can be attributed not to any one food factor but to generally improved nutrition of the children under the metabolic and environmental regimen.

SUMMARY

To one realizing the difficulties encountered in the biologic assay of food products for their vitamin D potency and the obscurity of the term "vitamin D units," the results of this investigation of the effect of irradiated contrasted with that of nonirradiated milk (judged by the average daily storage of nitrogen and acid-base minerals of well prepared and nutritionally stable children) come as no surprise. The fact that soft tissues may be growing more rapidly at one time and bone at another indicates the necessity of making different types of comparison of the metabolic data and not depending solely on the data concerning retention. From the standpoint of the actual average daily retention alone, it does not appear that the additional vitamin D in irradiated milk (90 to 96 and 180 to 190 U. S. P. units daily) had any nutritive advantage in the deposition of the minerals. On the other hand, the children showed a more rapid rate of growth in length during the periods when vitamin D was the only factor added. The increase in rate of skeletal growth was, in general, accompanied by a higher calcium-

21. Alberta Maloney, D.D.S., of the Dental Staff of the Children's Hospital of Michigan and the Children's Fund of Michigan, made all dental observations.

phosphorus ratio in the retention. This indicates a stimulus to formation of bone and, by the decrease in retention of nitrogen, phosphorus and sulfur, a shift from the formation of soft tissue to that of skeletal structure. Moreover, the variations which occurred in the average daily storage of calcium during the five day balance periods were reduced, which shows a regulating effect of the vitamin D during the administration of irradiated milk. In addition, all children were storing base in excess of acid while ingesting additional vitamin D, whereas several (J. H., D. P., W. P.) were actually storing more acid while taking nonirradiated milk, which again shows the development of skeletal structures. From the cumulative results just listed, it seems justifiable to conclude that vitamin D supplements in the form of irradiated milk included in a dietary known to be nutritionally good and given to children who have good health and good nutritive histories not only exert a regulating influence on the growth impulses but stimulate skeletal development. These problems emphasize, however, the need for more precise, less laborious methods and for further knowledge of the chemical and physiologic processes accompanying growth as well as of the physiologic effect of the administration of vitamin D to human beings.

ASTHMA IN CHILDREN TREATED WITH AUTOGENOUS (BRONCHOSCOPIC) VACCINE

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Chronic bronchial infection plays an important role in nearly every case of asthma in which involvement is severe enough and has lasted long enough. There is abundant clinical experience that vaccine therapy, whether by a specific or by a nonspecific mechanism, is useful in such cases. An autogenous vaccine has at least some claim to a specific factor, and such specificity is most certain if the culture is obtained directly from the bronchial tree through the bronchoscope.

The purpose of this paper is to report the result of therapy in 112 cases in which asthma in children was treated with an autogenous vaccine prepared from material removed through the bronchoscope.

The data presented here are the results of a study in which information was sought on the actual conditions in the tracheobronchial tree in asthmatic children. While a number of reports on bronchoscopic findings for adults have appeared, there have been few observations on children. Yet there was reason to believe, and the findings have proved, that bronchial infection played a more active and a more frequent role in asthma in childhood than in adult years. After the bronchoscope had been used for a few children without any difficulty or danger, it was decided to study a considerable series of children. It is here emphasized, however, that the use of the bronchoscope is not recommended as a routine procedure in the management of asthma in children.

In the allergy clinics of St. Christopher's Hospital for Children and the University of Pennsylvania, 223 children have been examined with the bronchoscope during the past five years. The examinations were performed by Dr. Gabriel Tucker and Dr. Emily Lois Van Loon.

No attempt was made to select cases because of any given age or sex of the patient or duration or origin of the disease. The 223 patients were observed consecutively, with only 4 exceptions. One child had moderately advanced progressive muscular dystrophy. The mother of 1 child refused to have the bronchoscopic study made. One patient was overlooked, and from 1 no secretion for vaccine could be obtained.

The bronchoscopic findings in the 223 cases will be made the subject of a separate publication.

The present report deals with the results of bronchoscopic autogenous vaccine therapy in 112 cases of the series. The children were selected from the whole group of 223 because they had been under our direct observation and treatment for at least six months. The remaining 111 children included many who returned to their referring physicians elsewhere for treatment and some who failed to return and of whose further course nothing is known.

TABLE 1.—*Age and Sex of Patients*

Age	Boys	Girls	Total
Under 1 year	2	1	3
1 year	6	1	7
2 years	7	1	8
3 years	3	4	7
4 years	3	6	9
5 years	6	7	13
6 years	5	6	11
7 years	12	4	16
8 years	9	1	10
9 years	7	0	7
10 years	4	1	5
11 years	7	2	9
12 years	0	2	2
13 years	3	2	5
Total	74	38	112

TABLE 2.—*Age at Onset of Asthma*

Age	No. of Cases	Age	No. of Cases
Under 1 year	28	8 years	4
1 year	16	9 years	1
2 years	6	10 years	4
3 years	11	11 years	2
4 years	7	12 years	0
5 years	4	13 years	0
6 years	9	None given (long standing involvement)	16
7 years	4		

These children varied in age from 6 months to 13 years. Three were under 1 year of age, 15 between 1 and 3 years, 29 between 3 and 6 years, 44 between 6 and 10 years and 21 in the 10 to 13 year age group.

Seventy-four (66 per cent) were boys, and 38 (34 per cent) were girls.

In 44 cases the asthmatic attacks had their inception during the first 2 years of life; in 24 they occurred first between the ages of 2 and 5 years; in 22, between 5 and 10 years, and in 6, between 10 and 12 years. For 16 children no specific time could be given by the mother. The best information we could obtain was that the child had had asthma for a "long time."

Many of the patients had had attacks of asthma over a considerable time. Eight children had had symptoms from seven and one-half to ten and one-half years, 17 from five to seven and one-half years, 18 from three to five years and 19 from one to three years. In only 33 cases was involvement under one year in duration.

Asthma was the only recognized allergic manifestation in 43 cases; 25 children had asthma and hay fever; 9 had asthma, eczema and hay

TABLE 3.—*Duration of Asthma*

Duration of Asthma	No. of Cases	Duration of Asthma	No. of Cases
Few weeks	18	6 years	2
6 months	15	6½ years	4
1 year	10	7 years	2
1½ years	1	7½ years	4
2 years	7	8 years	0
2½ years	1	8½ years	1
3 years	8	9 years	0
3½ years	3	9½ years	0
4 years	5	10 years	1
4½ years	2	10½ years	2
5 years	6	Long time	17
5½ years	3		

TABLE 4.—*Allergic Symptoms in Addition to Asthma*

Symptoms	No. of Cases
Asthma only	43
Hay fever	25
Hay fever and eczema	9
Eczema	10
Urticaria	4
Allergic rhinitis	4
Hay fever and allergic rhinitis	2
Migraine	2
Gastrointestinal symptoms	3
Hay fever and urticaria	1
Eczema, hay fever and gastrointestinal symptoms	1
Eczema, hay fever and urticaria	1
Eczema and angioneurotic edema	1
Hay fever and angioneurotic edema	2
Hay fever and migraine	1
Allergic rhinitis and urticaria	1
Migraine, hay fever and eczema	1
Eczema, allergic rhinitis, hay fever and gastrointestinal symptoms	1

fever, and 10 had asthma and eczema. Migraine, urticaria, allergic rhinitis and other symptoms appeared occasionally.

Study of our patients was begun in the usual fashion, with taking of a detailed history, careful physical examination, complete blood count, urinalysis and roentgen study of the chest.

The nose, throat, sinuses and ears were examined by the otolaryngologist, and a roentgen study of the sinuses was made if it seemed indicated.

Cutaneous tests for sensitivity to various substances, including foods and inhalants, were ordered.

Bronchoscopic study was made as soon as possible after the child came under observation. In each case aspirated material was sent to the laboratory for culture and preparation of vaccine.

The commonest feature of the history was the fact, stated by the mother, that asthmatic attacks came on as a rule in relation to "colds." This was the history in nearly every case. Moreover, the term "cold" was used by the mother to indicate not merely cough or sneezing but fever.

In 32 cases the asthma was also obviously related to hay fever, from which the children suffered at other seasons of the year. In 15 cases asthmatic attacks were known to follow the ingestion of certain foods.

Physical examination of the chests of these children revealed no evidence of pathologic change. In 2 cases there was a little increase in the size of the thymus gland. This, however, was so slight it was not found except by roentgen examination. One child showed a mild degree of emphysema.

TABLE 5.—*Results of Cutaneous Tests*

Results	No. of Patients
Substance produced positive reactions	
Food	94
Pollen	43
House dust	111
Animal epidermis	101
Other inhalants (orris, cottonseed, etc.)	74
All substances produced negative reaction	1

The following report of a roentgen examination is typical: There is a slight increase in the markings about the hili on both sides, which is compatible with a diagnosis of asthma.

The otolaryngologists, Dr. Harry P. Schenk and Dr. Edward H. Campbell, reported that 27 children needed tonsils and adenoids removed. They found sinus disease in 16 cases, deviated or irregular septums in 8, large turbinates in 1, chronic infection of the ear in 2 and acute infection in 1, granular pharyngitis in 2, large adenoid in 1 and tonsillar tags in 2. No nasal polyps were reported.

Each child was extensively tested for sensitivity to the usual foods and inhalants. One child consistently failed to react to cutaneous and intracutaneous tests, 2 reacted only to house dust, and 1 reacted to house dust and feathers, 1 to cat hair and feathers and 1 to house dust and wheat.

All the other children showed multiple cutaneous sensitivities.

It is to be remembered that the figures presented here refer only to the 112 asthmatic patients that were under our treatment for six months or longer. They do not refer to the whole group of 223 asthmatic children who were studied with the bronchoscope. The figures here

cited, therefore, cannot be applied to children's asthma in general. As before mentioned, the findings for the larger group are to be made the subject of another report.

The outstanding bronchoscopic finding in these 112 cases was purulent tracheobronchitis, observed in 72 cases. Early evidence of dilatation of the large tubes was found twenty-two times, and in 11 cases definite bronchiectasis was diagnosed. Two patients showed partial collapse of the bronchi on inspiration, and 4 were said to have normal bronchi. Three patients, in addition to other findings, had granulation tissue which bled when touched. All children showing signs of bronchi-

TABLE 6.—*Number of Bronchoscopic Examinations Per Child*

Number of examinations	1	2	3	4	5	6	8	25
Number of cases	45	26	21	10	4	4	1	1

TABLE 7.—*Bacteriologic Findings*

Number of Cultures Which Yielded	No. of Cases
1 organism	29
2 organisms	56
3 organisms	21
4 organisms	5
5 organisms	1
Total	112

Organisms Found in Pure Cultures	No. of Times
Streptococcus nonhaemolyticus	17
Streptococcus viridans	9
Staphylococcus albus haemolyticus	4
Staphylococcus albus nonhaemolyticus	4
Staphylococcus aureus haemolyticus	3
Streptococcus haemolyticus	2

Organisms Found in Cultures	No. of Times
Streptococcus nonhaemolyticus	71
Staphylococcus albus nonhaemolyticus	68
Streptococcus viridans	51
Streptococcus haemolyticus	20
Staphylococcus aureus nonhaemolyticus	20
Staphylococcus albus haemolyticus	14
Staphylococcus aureus haemolyticus	8
Pneumococcus	6
Diphtheroids	5
Bacillus influenzae	3
Micrococcus catarrhalis	2
Bacillus coli	1
Neisseria pharyngeus siccus	1
Hofmann-Löffler bacillus	1

ectasis were subjected to a bronchoscopic and roentgen study with iodized poppyseed oil.

In 20 cases so much purulent material was found in the tracheobronchial tree that the bronchoscopist suggested further aspiration. All of these had 4 or more bronchoscopic examinations. In these cases bronchoscopic drainage and topical applications of medication directly to the tracheobronchial mucosa, therefore, became an important part of the treatment.

Patients having only 2 or 3 bronchoscopic examinations were those who were studied further in order that it might be determined whether the bronchoscopic findings agreed with the clinical improvement.

The organisms cultured from material obtained with the bronchoscope are shown in table 7.

The table reveals a little variation in the vaccine used at the two clinics. One laboratory discarded all of the Staphylococcus albus. Nonhemolytic Staphylococcus aureus occurred twice. In the other hospital laboratory Staph. albus, hemolytic or nonhemolytic, was used with Streptococcus seventy times. In 4 cases nonhemolytic Staph. albus appeared in pure culture. In 2 cases hemolytic and nonhemolytic Staph. albus made up the vaccine, and in 3 cases a pure culture of hemolytic Staph. albus was used.

In several cases two or three vaccines were prepared per patient.

In table 8 are summarized the therapeutic procedures used for the 112 patients. In 27 cases administration of bronchoscopic vaccine was the only treatment used. In 3 cases, in addition to vaccine therapy,

TABLE 8.—*Treatment in Addition to Administration of Bronchoscopic Vaccine**

Type of Treatment	No. of Cases
Bronchoscopic vaccine alone	27
Bronchoscopic vaccine plus	
Bronchoscopic procedure	3
Tonsillectomy and adenoidectomy	3
House dust therapy	31
House dust therapy and bronchoscopic procedure	4
House dust therapy, tonsillectomy and adenoidectomy	3
Diet and bronchoscopic procedure	1
House dust and pollen therapy	5
House dust and pollen therapy and bronchoscopic procedure	3
House dust and pollen therapy, tonsillectomy and adenoidectomy	3
Pollen therapy	2
House dust and "inhalant" therapy	6
House dust and "inhalant" therapy and bronchoscopic procedure	2
House dust, pollen and "inhalant" therapy and diet	6
House dust, pollen and "inhalant" therapy, diet and bronchoscopic procedure	2
House dust therapy and diet	7
House dust therapy, diet and bronchoscopic procedure	4
Total	112

* In 1 case 4 bronchoscopic studies were made for diagnosis only.

repeated bronchoscopic procedures were performed, each time with aspiration of secretion and topical application of antiseptics. In 7 cases house dust was used together with vaccine, even if it had failed when used alone. In 12 cases house dust therapy was not instituted until a few months after the vaccine treatment. In 2 cases only a few doses of house dust were given, and in 1 it was administered at irregular intervals. In 2 cases pollen therapy was added because of pollen asthma. In cases of patients treated with vaccine, pollen and house dust, the house dust had failed when used alone for 2 of the patients, and it was not given 2 other patients until some time after the condition was well under control.

Vaccine treatment consisted in weekly subcutaneous injections of increasing doses, beginning with initial doses of 0.02 to 0.05 cc. The vaccine dilutions varied in the two hospitals. In one there were two dilutions, containing, respectively, 100,000,000 and 2,000,000,000 organisms per cubic centimeter; in the other there was only one dilution,

which contained 500,000,000 organisms per cubic centimeter. The increase of dosage was never more than 0.1 cc., and the largest quantity given was 1 cc. of a given dilution. After attainment of a maximum dose, in one hospital of 2,000,000,000 organisms and in the other of 500,000,000 organisms, the quantity was decreased and the interval gradually lengthened. An attempt was made to have the patient free from symptoms for six months to one year before the vaccine therapy was stopped. In cases observed over a period of years my co-workers and I have attempted to give five to six doses of vaccine at weekly intervals early in each fall and then once a month during the winter. We have been successful in getting cooperation from the mother in only 10 cases, because in the other cases the child was, in her words, "cured." We used bronchoscopic vaccine when any was available. In 5 cases we substituted stock vaccine.

The children were followed for periods varying from six months to five years. Only 13 cases fall in the six to twelve month period

TABLE 9.—*Time Under Observation*

Time Under Observation	No. of Cases	Time Under Observation	No. of Cases
Under 1 year	13	3½ years	8
1 year	21	4 years	11
1½ years	17	4½ years	7
2 years	12	5 years	3
2½ years	8	5½ years	1
3 years	13		

of observation. In 67 cases the children have reported for one to three years, in 19 from three to four years and in 11 from four to five and one-half years.

Obviously, in the treatment of asthmatic children one is not justified in strictly adhering to the conditions of a purely scientific experiment. Comparatively few children received a single form of treatment to the exclusion of all others. In many cases several therapeutic measures were employed. It is therefore difficult to assign to any one form of treatment a definite value in terms of percentages.

It is not wholly impossible, however, to arrive at some estimate of the value of the bronchoscopic vaccine in our 112 cases. There is, in the first place, the group of 27 children for whom bronchoscopic vaccine therapy was the only method of treatment used. For purposes of clarity I shall call them group 1.

In this group the youngest child was 6 months and the oldest 13 years of age. Fifteen patients had had asthma for a year or less, and 12 had had symptoms for between two and ten and one-half years.

Only 3 patients had been reporting for less than a year. Ten patients were followed for between two and one-half and four and one-half years, while the others were seen for one to two years.

Fourteen patients had no asthma at all during the period of observation. In 2 cases attacks were numerous during the first two years; in 1 there has been no attack for the past year and in 1 no asthma for the past two and one-half years. Similarly, 1 patient had asthma for nine months and then none to the time of writing, a three and one-half year period. One child had asthma associated with "colds" three times during the first eighteen months but no asthma for the past year.

One child is still wheezing, but so little that the mother refuses to bring the patient for more treatment. In this case there is a complicating deformity of the epiglottis.

One child drank iced lemonade on a hot day and had asthma a few minutes later. He has not reported since.

One child had an attack at the end of the first year but has had none for the past three years.

One child had asthma twice in two years, once after playing with a dog for the first time and once after the application of liniment to her chest.

The remaining 5 children had one or two asthmatic attacks during the first two months after the bronchoscopic procedure and none after that.

The results in the 27 cases during the period of observation were as follows: Complete relief was obtained in 23 cases, great improvement in 1 case and doubtful results in 3 cases.

Of the 31 patients who received only house dust in addition to bronchoscopic vaccine, 5 had received dust previously without satisfactory results. In these 5 cases 1 child has had complete relief for two years, 2 children for two and one-half years, 1 for only four months and 1 for ten months, except for some asthma associated with hay fever.

In 7 of the 31 cases in which the patient was treated with house dust, the dust was added after several months of therapy. Here complete relief was obtained in 6 cases. One child had asthma associated with untreated pollinosis.

In 3 cases only a few doses of house dust were given. One patient had complete relief and 1 apparently failed to benefit, although during the last five months of her four year period of observation she has been free from symptoms. The third patient left the clinic at the end of the pollen season. She had been free of asthma until symptoms of hay fever developed, associated with asthma for the first time, and she consequently became discouraged.

Two patients had pollen therapy (for known hay fever) together with the bronchoscopic vaccine. Both children were completely relieved.

It seems from the data just cited that the bronchoscopic vaccine may be credited with some part of the benefit derived in 17 cases (group 2). The results in these cases were as follows: Complete relief was obtained in 13 cases, complete relief except for pollen sensitivity in 3 cases and apparent failure in 1 case.

In the remaining 68 cases (group 3) repeated bronchoscopic procedures undoubtedly played a part in relieving 19 patients, house dust therapy 14 and removal of feather pillows 18. Food was a definite factor in 3 cases and a possible source of trouble in 14 others. The results in group 3 were as follows: Complete relief was obtained in 42 cases, marked relief in 13 cases, doubtful relief in 9 cases and failure in 4 cases.

As has been noted, 5 patients, although showing some improvement, have not been free of attacks for a sufficiently long period to be classified except as failures.

1. Russell, aged 2 years (asthma), under observation eighteen months, shows marked improvement at the time of writing but still has mild attacks with some of his colds, although there is no asthma with others. Because of illness in the family, treatment (house dust extract and vaccine) was interrupted a great deal.

2. Dorothy, aged 18 months (asthma), was under observation four and one-half years. She had only one attack the first year, a second attack at the end of two years and three attacks in the following year. She had 6 bronchoscopic examinations in this four and one-half year period. The first 2 and the last 2 examinations showed considerable mucopurulent secretion. Results of the third and fourth were negative. The child comes from a poor home and reported irregularly at clinic. She had many intercurrent infections. The attacks are now much less severe and shorter in duration.

3. John, aged 7 years (asthma), failed to benefit from a vaccine made from nasal secretion and house dust extract. He has improved greatly since the bronchoscopic vaccine was added. He had three attacks of asthma associated with a cold in the winter of 1937 and only one in the winter of 1938. Every week during the summer of 1937 he had asthma associated with sneezing. He is having pollen therapy this year.

4. Alice, aged 2 years, was under observation only two years. She was treated with house dust extract, vaccine and elimination of reactors in the food and inhalant group. There was poor cooperation from the family. She had no attack of asthma from November 1934 to October 1935. The previous year she had had five attacks. The family did not report after December 1935.

5. Barbara, aged 7 years, was under observation four and one-half years. She had severe asthma, eczema and hay fever when she was first seen. She had been treated with house dust extract and diet previously, with poor results. She continues to have frequent attacks of asthma due to such factors as food, smoke, dust, weather, pollen and colds. However, all symptoms are greatly improved. The child has been treated with diet, house dust extract, pollen, elimination of feather pillows and attempted desensitization with cottonseed extract. She had had 25 bronchoscopic examinations, each showing a chronic inflammatory process with profuse purulent secretion and at times granulation tissue which bled easily. Although attacks continue, the child has improved greatly.

Certain clinical impressions have been formed in the course of this work.

1. Bronchoscopic procedure provided prompt although temporary relief to the patients.

2. In 33 of the 112 cases the asthma did not return after administration of bronchoscopic vaccine was started (twelve to fourteen days after the bronchoscopic examination).

3. The good results of the vaccine were directly proportional to the length of time the vaccine was given. When therapy was stopped after four to six months there was a decided tendency for the patient to relapse.

4. Reactions to vaccine therapy apparently occurred in 11 cases. In each case asthma developed within twelve hours after the administration of the vaccine. In 2 cases the attacks were moderately severe and lasted twenty-four hours. The others were readily controlled with ephetonine. In 2 cases the reaction occurred several times, in 1 after every increase in the dose. Nine children had asthma only once after vaccine therapy.

5. The bronchoscopic procedure was well tolerated; only a single complication in all of the 223 cases was witnessed, and this may have been a coincidence rather than a complication.

6. When the children who had had bronchoscopic vaccine contracted "colds," they usually did not contract asthma, reversing the findings reported in the histories.

7. Use of stock vaccine in a group of control cases would have added to the value of this study, without question. This, however, was omitted. I can only offer the statement that 12 children had previously had unsuccessful treatment with stock vaccine.

CONCLUSIONS

1. Bronchial infection with purulent tracheobronchitis, as seen on bronchoscopic examination, is far more frequently present in asthmatic children than in asthmatic adults.

2. Vaccine therapy therefore becomes an important part of the treatment of asthmatic children.

3. Bronchoscopic examination is not harmful.

4. Bronchoscopic study itself exerts a beneficial effect and in addition permits obtaining of uncontaminated material for culture and preparation of vaccine.

5. Vaccine therapy, for optimum results, should be continued until the patient has been free from symptoms for a year.

BASAL METABOLISM OF TUBERCULOUS CHILDREN

III. TUBERCULOSIS OF BONE

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In previous studies of the basal metabolism of tuberculous children, it was found that of 143 children with pulmonary tuberculosis of the primary, or childhood, type, 96 per cent had increased basal metabolism even in the presence of a normal temperature.[1] Serial studies made on 20 of these children over periods ranging from six months to three years revealed that the basal metabolism remained high as long as the tuberculous process remained active, as evidenced by physical signs, positive roentgenographic findings and an increased sedimentation rate. When the infection became inactive, the basal metabolism fell to a normal level.[2]

It was concluded from these studies that the basal metabolic rate is an additional criterion of the activity of a primary tuberculous lesion. In the presence of a normal temperature, high basal metabolism indicates that the tuberculous process is still active; a return to normal metabolism indicates that the lesion has become inactive.

So consistent were these findings that for children with previously active pulmonary tuberculosis of the childhood type normal basal metabolism is a prerequisite for discharge from Sea View Hospital.

When clinical symptoms of tuberculosis are present, no additional proof of activity of the process is needed. The question of activity without clinical symptoms, however, is often equivocal. There is no one reliable measure of a tuberculous process. The allergic reactivity, the sedimentation rate of the erythrocytes, the blood count and the roentgenogram do not parallel the activity of the infection. Therefore, any additional criterion for determining activity is of clinical importance.

Since it was found that the basal metabolism can be used as such an additional criterion of activity of primary pulmonary tuberculosis,

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From the Pediatric Service of Dr. Bela Schick, Sea View Hospital.

1. Topper, A., and Rosenberg, H.: Basal Metabolism of Tuberculous Children, Am. J. Dis. Child. **52**:266 (Aug.) 1936.

2. Topper, A., and Shore, J.: Basal Metabolism of Tuberculous Children: II. Afebrile Primary Pulmonary Tuberculosis, Am. J. Dis. Child. **58**:119 (July) 1939.

the question arose whether such a criterion can be used also in cases of tuberculous infection of other types.

This question has been investigated at Sea View Hospital, where an unusual opportunity is afforded for studying children with tuberculosis of all types and in all stages.

Of 115 afebrile children with the reinfection, or adult, type of pulmonary tuberculosis, 80 per cent were found to have normal basal metabolism. In this respect children with the adult type of tuberculosis are similar to adults with the same type of infection. Evidently the basal metabolic rate cannot be used diagnostically to determine the activity of this type of lesion.

Of 43 children with tuberculous pleurisy, 26 were found to have an increased and 17 a normal metabolic rate. The pleural reaction may be associated with primary pulmonary tuberculosis or with the reinfection type of the disease, and until cases of tuberculous pleurisy have been studied over sufficiently long periods to determine the underlying pathologic condition, we prefer merely to mention them in this paper, without discussing the results.

A preliminary study of a small group of children with tuberculosis of bone seemed to show that the metabolism was increased in children with actively draining sinuses and normal in children with apparently inactive infections. However, in our preliminary report we indicated that this group was not large enough and had not been studied long enough to warrant drawing any conclusions.

Since this preliminary report, we have made extensive determinations of the basal metabolism of 50 children with tuberculosis of bone both in the frankly active and in the apparently inactive stage. All these children were afebrile at the time of study and for long periods before and after study. Some of them have been followed for one and two years. This paper reports the results of our investigations. The purpose of these investigations was to determine whether the basal metabolism could be used in the diagnosis of activity of tuberculosis of bone.

The data collected in these studies may be seen in the table. The basal metabolism is recorded as total calories per twenty-four hours. Since most of the children had marked deformity or were wearing a cast at the time of study, many of their body measurements are either lacking or inaccurate. In the absence of accurate measurements, the usual standards of metabolism, referring to height, sitting height, weight and surface area, could not be applied. The total metabolism was therefore compared with the expected metabolism referred to age.[3] While this standard is not ordinarily applied, it is occasionally used, notably in

3. An exhaustive discussion of this standard of metabolism is given in the article by F. G. Benedict and F. B. Talbot (Metabolism and Growth from Birth to Puberty, Publication 302, Carnegie Institution of Washington, 1921).

Basal Metabolism of Afebrile Children with Tuberculosis of Bone

Patient	Sex	Age, Years	Height, Cm.	Sitting Height, Cm.	Weight, Kg.	Pulse Rate	Test Temperature	B. M., Total Calories 24 Hr.	Basal Metabolic Rate	E. S. R., Mm. in 1 Hr.	Diagnosis
1. H. A.	♀	5	100	56	15	98	98.4	827	Increased	72	Tuberculous dactylitis; generalized tuberculous adenopathy; chronic phlyctenula; scrofuloderma plus generalized tuberculous adenopathy; lungs normal
		6	107	60	18	82	98.4	852	Increased	25	
2. S. A.	♂	14	In cast			88	98.4	1,332	Normal	5	Pott's disease of lumbar spine; lungs normal; active
3. M. C.	♀	10	In cast			100	99	1,106	Increased	30	Tuberculosis of dorsal part of spine; primary pulmonary tuberculosis, active
4. A. A.	♀	11	Deformity		28	72	99.6	950	Low normal	5	Tuberculosis of lumbar part of spine and sternum; lungs normal; active
5. B. B.	♀	5	112	60	18	102	99.2	921	Increased	39	Tuberculosis of left ankle; primary pulmonary tuberculosis
		6	117	65	23	96	99	1,071	Increased	29	Tuberculosis of left ankle; primary pulmonary tuberculosis
		7	120	66	25	88	99	935	Normal	8	Tuberculosis of left ankle; lungs healed; calcification
6. R. G.	♀	10	Deformity			100	98	1,205	Increased	28	Tuberculosis of dorsal part of spine; primary pulmonary tuberculosis
7. J. C.	♂	6	117	65	20	84	99.6	664	Normal	5	Tuberculosis of right femur; lungs normal; active
8. M. D.	♀	12	148	78	40	86	99.4	1,250	Normal	14	Spina ventosa; lungs normal; healed tuberculosis of mesenteric glands
9. R. H.	♂	5	In cast			100	98	769	Increased	2	Tuberculosis of left hip; tuberculosis of hilar gland
10. A. D.	♀	15	151	82	40	104	100	1,344	Normal	38	Tuberculosis of right hip; tuberculosis of ribs with draining sinus; chest normal
11. A. D.	♀	6	116	61	23	98	98.6	908	Increased	38	Tuberculosis of right hip; active primary pulmonary tuberculosis
		8	126	67	29	72	98.2	843	Normal	7	Tuberculosis of hip; healed primary complex
12. J. E.	♀	10	...	63	21	104	100	984	Normal	112	Tuberculosis of right elbow, with sinus; tuberculosis of right ankle; lungs normal; multiple cold abscesses
		13	...	..	23	100	100	1,145	Low normal	88	Tuberculosis of left hip with sinus; lungs normal
		14	...	..	..	86	98	1,164	Low normal	77	Tuberculosis of left hip with multiple sinuses; lungs normal
13. E. P.	♂	10	140	76	37	100	99.2	1,382	Increased	51	Tuberculosis of both hips; active primary pulmonary tuberculosis
		12	...	..	..	100	98	1,205	Normal	31	Tuberculosis of left shoulder; lungs clear
14. H. F.	♀	13	139	72	31	96	100	1,104	Low normal	10	Tuberculosis of spine; chest normal
15. A. G.	♂	5	...	..	14	100	99	561	Normal	10	Active tuberculosis of left knee; healed tuberculosis of lungs
16. G. H.	♀	13	...	..	..	110	101	1,123	Low normal	92	Tuberculosis of left humerus; tuberculosis of left hip, with sinus; healed primary complex
17. A. G.	♀	14	156	84	54	82	98	1,395	Normal	20	Tuberculosis of right femur, inactive; chest normal
18. M. H.	♀	10	...	..	19	100	101	1,036	Normal	6	Tuberculosis of spine, with sinus; adult type pulmonary tuberculosis
19. M. H.	♀	9	...	..	20	88	98	914	Normal	18	Tuberculosis of dorsal part of spine; chest normal
		10	...	..	..	84	98.2	917	Normal	17	Tuberculosis of dorsal part of spine; chest normal
20. E. H.	♂	10	...	..	19	89	98	1,066	Normal	74	Tuberculosis of left hip, with sinus; calcified lungs
21. R. J.	♂	5	102	55	17	90	98	842	Increased	35	Tuberculosis of dorsal part of spine; pleural effusion
		6	109	56	19	80	99	864	Increased	7	Paravertebral abscess; primary tuberculosis

22. M. J.	♀	15	163	85	46	80	97.4	1,286	Low normal	26	Tuberculosis of right elbow; pneumothorax; adult tuberculosis
		16	165	86	54	82	98	1,479	Normal	21	Tuberculosis of left elbow; right phrenectomy; adult tuberculosis
23. J. K.	♂	16	...	..	55	80	97.8	1,203	Low normal	31	Tuberculosis of lumbosacral spine, with sinus; adult type pulmonary tuberculosis
24. P. K.	♀	8	116	..	17	90	99	1,008	Increased	39	Tuberculosis of left hip, with sinus; active primary pulmonary tuberculosis
		9	122	..	19	100	98.2	875	Normal	24	Lungs clear
25. H. L.	♂	10	...	..	..	82	98	1,034	Normal	122	Tuberculosis of left hip, with sinus; lungs clear
26. J. L.	♀	15	...	..	40	90	99	1,368	Normal	10	Tuberculosis of dorsal part of spine; chest normal
27. V. M.	♀	13	142	75	33	92	99.2	1,181	Low normal	30	Tuberculosis of left hip, healed; lungs clear
28. I. M.	♀	14	152	81	..	99	100	1,423	Normal	8	Pott's disease, healed; adult type pulmonary tuberculosis with pneumothorax
29. M. M.	♂	13	141	71	34	108	101	1,224	Normal	46	Tuberculosis of sternum, with sinus; tuberculosis of spine; adult type pulmonary tuberculosis
30. V. N.	♀	16	...	..	..	86	98.6	1,308	Low normal	107	Right hip in cast; chest normal
31. E. N.	♂	10	140	71	30	78	99	1,056	Normal	10	Tuberculosis of right os calcis; chest normal
		12	148	78	52	80	98.6	1,266	Normal	12	Tuberculosis of right os calcis; chest normal
32. A. P.	♂	15	155	76	41	96	100	1,447	Normal	20	Tuberculosis of spine with multiple sinuses; lungs normal
33. J. P.	♀	6	...	62	..	96	99.8	1,017	Increased	27	Tuberculosis of left hip; bilateral sacroiliac tuberculosis; pleural effusion
34. S. P.	♀	8	...	..	17	90	98	934	Increased	9	Spinal tuberculosis; tuberculosis of hilar gland
		9	...	..	18	100	99	1,109	Increased	9	Spinal tuberculosis; large masses abdominal glands; chest normal
35. M. P.	♂	10	...	..	20	88	97.2	973	Normal	7	Tuberculous spondylitis; chest normal
36. E. P.	♂	11	...	..	23	82	98	972	Low normal	12	Pott's disease; healed tuberculosis of chest
37. J. P.	♀	6	...	..	18	100	100	881	Increased	116	Tuberculosis of lumbar part of spine; primary pulmonary tuberculosis
38. G. P.	♀	8	120	64	20	96	98	804	Normal	6	Tuberculosis of right tibia; spina ventosa; chest normal
39. R. R.	♀	12	...	..	39	88	99	1,272	Normal	18	Tuberculosis of left hip; chest normal
40. N. R.	♀	8	...	..	20	98	99	868	Normal	6	Pott's disease with cold abscess; chest normal
41. D. R.	♀	12	...	..	42	100	98	818	Low	19	Tuberculosis of spine with multiple sinuses; calcified primary complex; tuberculous peritonitis
42. M. S.	♀	9	131	71	31	100	100	1,308	Increased	67	Tuberculosis of right humerus, with sinus; sacroiliac tuberculosis; primary pulmonary tuberculosis
43. F. S.	♂	9	...	..	21	86	98	888	Normal	10	Tuberculosis of spine; chest normal
		11	...	..	..	..	....	1,031	Normal	25	Tuberculosis of dorsal part of spine; chest normal
44. R. S.	♂	8	120	64	..	84	98	820	Normal	21	Tuberculosis of right knee; in cast; chest normal
45. P. T.	♂	10	131	68	30	82	98	1,043	Normal	12	Tuberculosis of left hip with sinus; chest normal
46. T. T.	♀	12	141	71	36	86	98	1,074	Low normal	10	Tuberculosis of right hip and dorsal part of spine; chest normal
47. B. V.	♀	11	...	..	20	96	99.8	1,080	Normal	6	Tuberculosis of dorsal part of spine, healed; tuberculous dactylitis; chest normal
48. K. W.	♀	6	113	64	15	110	99.2	1,027	Increased	46	Tuberculosis of left elbow with sinus; primary tuberculosis of lung
49. E. W.	♀	10	128	70	30	100	100	1,045	Normal	51	Tuberculosis of lumbar part of spine; chest normal
50. T. P.	♂	10	...	..	22	100	98.6	1,035	Normal	30	Healed tuberculosis of dorsal part of spine; active tuberculosis of metatarsal bone; lungs normal

measuring the efficacy of thyroid therapy for cretins.[4] Again, in a study of the metabolism of undersized but otherwise normal children, this standard seemed to reflect their normal metabolic processes, whereas all other standards seemed inapplicable.[5]

Column 9 of the table indicates whether the metabolism was considered in a general way to be normal, low or high for the age of the child.

It may be seen from the table that of the 50 children with tuberculosis of bone 36 had normal basal metabolism, irrespective of whether the lesion was frankly active or apparently inactive. In this group the sedimentation rate of the erythrocytes did not parallel the metabolism. In fact, even in cases in which there was low grade fever (temperatures up to 100 or 101 F.) the metabolism was not increased (cases 10, 12, 14, 16, 18, 28, 29, 32 and 49). Similarly, in 10 cases in which there were actively draining sinuses the metabolism was normal (cases 12, 16, 18, 20, 23, 25, 29, 32, 41 and 45).

In 14 children the metabolism was found to be increased. Since the temperature of these children was for the most part normal and the bone lesions similar to those of the 36 children with normal metabolism, further analysis was made to determine the cause for the increased metabolism. It was found that of the 14 children with increased metabolism, all except 2 (cases 1 and 34) had active pulmonary tuberculosis of the primary type. This finding was consistent with our previous finding of increased metabolism in this type of tuberculosis. Serial studies in some of these cases showed that when the tuberculous process in the lungs became inactive the metabolism returned to a normal level, irrespective of whether the bone lesion was active or inactive (cases 5, 11, 13 and 24).

It seems, then, that the basal metabolism of children with tuberculosis of bone is not increased unless there is an associated primary active pulmonary lesion. For diagnosis of activity in a bone lesion one must depend on the roentgenogram, the leukocyte count, the sedimentation rate and clinical signs and symptoms of activity. The finding of increased metabolism in an afebrile child with tuberculosis of bone indicates an active primary lesion in the lung and is therefore a valuable diagnostic aid.

That the basal metabolic rate is not increased in tuberculosis of bone may be understood when the nature of the process is considered. Tuberculous bone lesions are exceedingly chronic, with little or no tendency to formation of new bone. Reparative processes are limited mainly to the production of fibrous tissue. "Cold" abscesses, when they develop,

4. Talbot, F. B.: Physiol. Rev. **5**:477, 1925.

5. Topper, A.: Standards of Basal Metabolism for Children of Retarded Growth, Am. J. Dis. Child. **45**:1203 (June) 1933.

give rise to no local or general increase in heat—a fact which has determined their name.

An increase in metabolism associated with toxic destruction of protein occurs more or less in all infections. The more toxic the condition, the greater the destruction of body protein and therefore the higher the metabolism. In tuberculosis, even when fever is present, the metabolism has been found to be relatively lower than it is in other infections with the same degree of fever.[6] Investigators have concluded that this may be due to the fact that in this disease there are often few signs of toxemia and only slight destruction of protein. The excretion of nitrogen, which may be taken as an index of protein destruction, although higher than normal, is lower in tuberculosis than it is, for example, in pneumonia, typhoid, erysipelas or scarlet fever. McCann and Barr [7] found a normal specific dynamic action in tuberculosis. In conditions in which great destruction of protein has occurred—for example, typhoid fever—the specific dynamic action is decreased, since the ingested protein, instead of being burned, is used to replace exhausted protein stores. The normal specific dynamic action in tuberculosis affords evidence that the protein stores of the body have not been depleted. Evidently destruction of body protein with absorption of toxins is, as a general rule, at a minimum in this disease. Cases of adult tuberculosis in which high metabolism has been reported have been for the most part cases of severe infection and great toxicity. Gräfe [8] found high metabolism in 7 severely ill tuberculous adults studied in a respiration chamber. McMahon and Klein [9] found a definite increase in the metabolic rate in a group of patients with far advanced tuberculosis, while those with incipient or moderately advanced disease had normal metabolism.

In primary tuberculosis of the lungs, the increase in the basal metabolic rate was evidently not due to destruction of protein, since most of the children were afebrile and atoxic and were gaining in weight, an accomplishment manifestly impossible in the face of great loss of protein. What, then, accounts for the increased metabolism as opposed to the normal metabolism found in the other types of tuberculosis studied?

It has been said that "the lymphatic system is the great common repository for the initial infective dose of the tubercle bacilli," [10] and in

6. DuBois, E.: Basal Metabolism in Health and Disease, Philadelphia, Lea & Febiger, 1927, p. 389.

7. McCann, W. S., and Barr, D. P.: Clinical Calorimetry: Metabolism in Tuberculosis, Arch. Int. Med. **26**:663 (Dec.) 1920.

8. Gräfe, E.: München. med. Wchnschr. **47**:1081, 1920.

9. McMahon, A., and Klein, H. A.: J. Missouri M. A. **26**:586, 1929.

10. Stewart, C. A.: Tuberculosis, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., vol. 2, chap. 28, p. 14.

this fact probably lies the answer to our query. In this connection it should be noted that in other diseases involving lymphatic tissue, notably the leukemias, the general metabolism is increased even when the temperature is normal. In conditions associated with splenomegaly (part of the reticuloendothelial system) there is often an increased basal metabolism.[11] In cases 1 and 34 of the present series, the metabolism was increased. Here the only "different" factor was the involvement of lymphoid tissue. Similarly, in 3 children whose cases are not reported here, who had tuberculous adenopathy with no active involvement of either lungs or bone, we found increased metabolism.

The metabolic activity of lymphoid tissue has been extensively studied by Warburg and his co-workers.[12] These investigators found that lymphadenoid tissue has high metabolic activity, ranking between embryonic tissue and nonmalignant tumor tissue in this respect. It was further found that when lymph tissue grows beyond its normal dimensions, its glycolytic activity increases tremendously. In fact, the metabolic activity of excised enlarged noninflammatory tonsillar tissue was found to be as great as that of tumor tissue.

The childhood type of pulmonary tuberculosis is distinguished by its predilection for lymphatic tissue. An intensive reactivity of the lymphatic system is always associated with this type of infection. Even when the primary complex is small, the involvement of lymph glands is extensive.[13]

The adult type of tuberculosis shows a more localized reactivity, with little involvement of regional lymph glands. Fixed tissue cells, especially connective tissue and epithelioid cells, are involved to a much greater extent. The metabolism of adult connective tissue has been found to be minimal, as is that of resting epithelium. Unless, therefore, there is great toxic destruction of protein, the general metabolism is not increased in this type of infection.

Similarly, bone is an inert tissue, and the metabolic activity of erythrocytic bone marrow is low.[14] It is only when the myeloid-erythroid ratio of bone marrow increases that its metabolic activity increases—a fact which may possibly explain the increased metabolism associated with the leukemias. In tuberculosis of bone, therefore, unless the condition is associated with severe toxemia, the general metabolism remains normal. And since toxins are usually extruded by way of chronic sinuses, their absorption is at a minimum here, and severe toxemia is unusual. When increased basal metabolism is present, one must look for an active primary lesion in the lung to explain the increase.

11. Topper, A.: Acta pædiat. **16**:189, 1933.
12. Warburg, O.: The Metabolism of Tumors, London, Constable & Co., Ltd. 1930.
13. Schick, B.: M. Clin. North America **20**:719, 1936.
14. Warren, C. O.: Am. J. Physiol. **110**:61, 1934.

A primary lesion in the lung involves lymphatic tissue, with increased functional activity of such tissue. Increased functional activity of organs has been found to be accompanied by increased oxygen consumption of the tissues in those organs.[15] Increased oxygen consumption of the tissues is reflected in increased general metabolism. It is not surprising, therefore, to find an increased metabolic rate in active primary pulmonary tuberculosis.

SUMMARY AND CONCLUSIONS

Previous studies of afebrile tuberculous children showed that the basal metabolism could be used diagnostically to determine the activity of a primary infection. It was found that the basal metabolic rate remained high as long as the tuberculous lesion was active, as evidenced by physical signs, positive roentgenographic findings and an increased sedimentation rate. When the infection became inactive, the basal metabolism fell to a normal level.

A group of children with the adult type of tuberculosis were found to have normal metabolism.

The present study was made to see whether this criterion of activity could also be used for children with tuberculosis of bone. Fifty afebrile children were studied, some for periods of one and two years. Of these, 36 were found to have normal metabolism, irrespective of whether the tuberculous lesion was frankly active or apparently inactive. Fourteen children had increased basal metabolism. Of these, 12 had an active primary pulmonary lesion.

This emphasized the fact that an increased basal metabolic rate in the presence of a normal temperature can be used as an additional criterion of activity of pulmonary tuberculosis of the childhood type. It was further concluded from this study that when an afebrile child with a tuberculous bone lesion is found to have increased basal metabolism, the presence of an active primary pulmonary lesion should be suspected.

The cause for increased metabolism in the childhood type of pulmonary tuberculosis as opposed to normal metabolism in other types of the infection is probably related to the extensive involvement of lymphatic tissue in this type of tuberculosis. The oxygen consumption of lymphatic tissue has been shown to be high, and it is especially so when the functional activity of such tissue is increased.

15. Deutsch, W., and Raper, H. S.: J. Physiol. **87**:275, 1936.

FAMILIAL CLEIDOCRANIAL DYSOSTOSIS (CLEIDAL DYSOSTOSIS)

A PREOSSEOUS AND DENTINAL DYSTROPHY

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A family with four members who have defective or missing clavicles is unusual, as only a few such families have been described. However, the condition is not a recent discovery. The first case of these defects was recorded as early as 1766 by Morand.[1] The first familial occurrence was reported over a century later by Cutter[2] (1870). Because in all cases the contour of the skull showed a change, the name cleidocranial dysostosis was proposed by Marie and Sainton[3] (1897). Involvement of more than one member of a family has occurred relatively frequently, and the total number of cases of hereditary or sporadic occurrence reported in the world literature is more than 130. Most reports have emphasized that the changes in these cases were inherent in membranous bones, but Fitchet[4] in 1929 called attention to the fact that since the clavicles are formed from both cartilage and membrane both kinds of bones are affected. From a review of published cases and an intimate study of four members of one family, it is apparent to us that all bones formed in cartilage, as well as those formed in membrane, may be and usually are affected. These findings for the most part have not been described in previous reports but we believe they were present. The family to be discussed, which we think presented manifestations representative of the entire group of cleidocranial dysostosis, is of interest not only because of the unusual demon-

From the Children's Memorial Hospital.

1. Morand: Observations anatomique, Hist. Acad. roy. d. sc. [de Paris] **4**: 47, 1766.

2. Cutter, E., in Jackson, J. B. S.: A Descriptive Catalogue of the Warren Anatomical Museum of Harvard University, Boston, A. Williams & Co., 1870, no. 217.

3. Marie, P., and Sainton, P.: Observation d'hydrocéphalie héréditaire (père et fils) par vice de developpement du crâne et du cerveau, Bull. et mém. Soc. méd. d. hôp. de Paris **14**:706, 1897.

4. Fitchet, S. M.: Cleidocranial Dysostosis: Hereditary and Familial, J. Bone & Joint Surg. **11**:838, 1929.

stration of four members with the condition but because the ages of the affected members offer a panorama of the changes that may be expected at different age periods in a single person. To emphasize the developmental changes associated with the clavicular defects is the main purpose of this report.

REPORT OF CASES IN A FAMILY

The Pappas family, of Greek extraction, enjoyed life as does any normal family. An affected member was not handicapped in any way. He was not conscious of bony defects within his body. The father and three daughters, of a family of nine, were short and had shoulders which sloped markedly. All four had a distinct resemblance to each other. The mother was a well developed woman of normal appearance, and four other children (boys and girls) were slender; all five in no way resembled the slightly dwarfed members. This unusual condition first attracted attention when the daughter Elaine, aged 14 years, came to one of us (R. G. H.) because of the worn and broken condition of the teeth and because of delay in the eruption of the permanent teeth. The unusual finding that the entire set of deciduous teeth were retained at an age when all should have been shed and replaced led to a further investigation. It was revealed that younger sisters, Patsy, aged 5, and Vivian, aged 11, had similar dental defects. The father stated that he had retained his deciduous teeth until the age of 30 years and that they had then been replaced with a plate because of their worn condition.

This led to still further investigation of the family and ultimately to roentgen studies of the entire group. This revealed that Vivian and Lorraine had many osseous defects, apparently varying from one another only because of the difference in age and development. The father and the three daughters had midline grooves of the skull, partial or complete absence of the clavicles, irregular positions of unerupted teeth and changes at the junction of cartilage and bone and at the sutures. The latter were especially noticeable in the skull and at the symphysis pubis, where there was marked delay in ossification (fig. 4). The epiphysial lines and sutures, as recognized on roentgenograms, were wide, apparently being made up of more cartilage or membrane than normal. The digits were shortened, especially the great toes and the thumbs. The fingers were tapered at the end because of the narrowing of the distal phalanges, over which longitudinal wrinkles were found. Slightly flared metaphyses, coxa magna and genu valgum were present. Also the second metacarpal bone was slightly overgrown in Lorraine, and the proximal epiphysis of the middle phalanx of the little finger was enlarged in the two younger children, Patsy and Vivian. In addition to a general change in the shape of the skull, which was characterized by wide bosses, prominent frontal eminences, prognathism, a median furrow and delayed closure of the sutures in the children, there were many wormian bones along the lambdoidal sutures (fig. 2). The delayed ossification was not associated with overgrowth or marked distortion at the zones of proliferating cartilage or of membrane. The transition from cartilage to bone took place very slowly. Slight rickets-like deformities were present in this group of four and were conspicuously absent in the other members of the family.

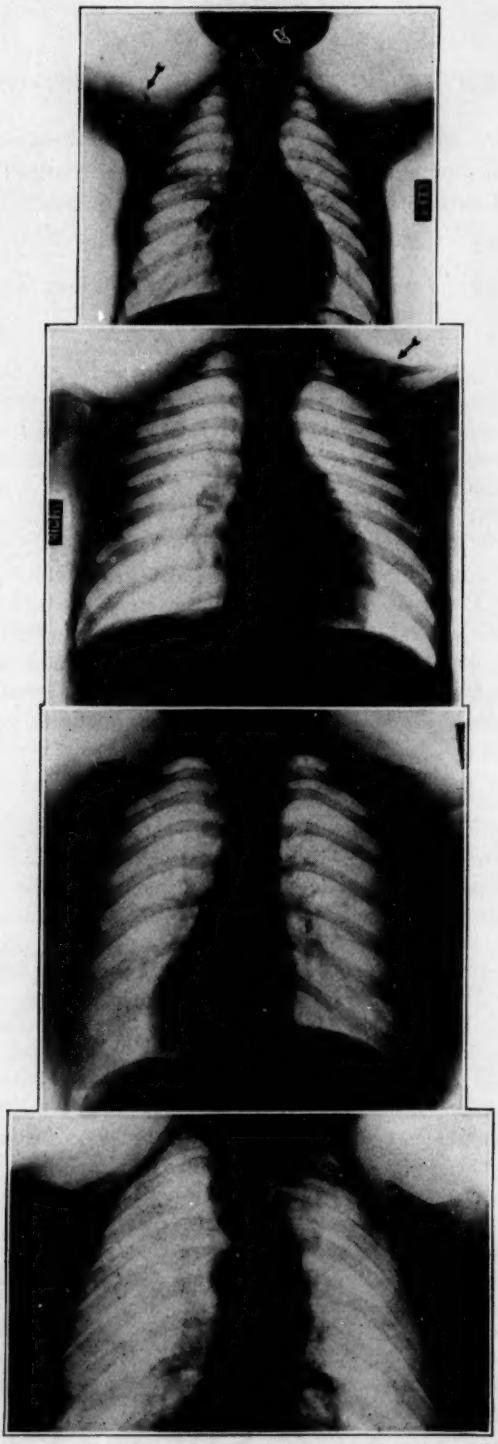

Fig. 1.—Roentgenograms of the afflicted members of the Pappas family: Patsy, aged 5 years; Vivian, aged 11; Elaine, aged 14 and the father, John, aged 61. Elaine and John are without clavicles. The two other daughters have rudimentary portions of the clavicles (arrows). Vivian has a false joint near its center. Parts of the clavicle are derived from both membrane and cartilage. The absence of the entire clavicle indicates that there is partial agenesis of both kinds of bone.

The deciduous teeth showed moderate caries, and in the older children they were in need of repair because of broken areas due to wear. When Elaine was 13 years old many of the deciduous teeth had been removed in the hope of permitting eruption of the permanent teeth. The permanent tooth buds occupied

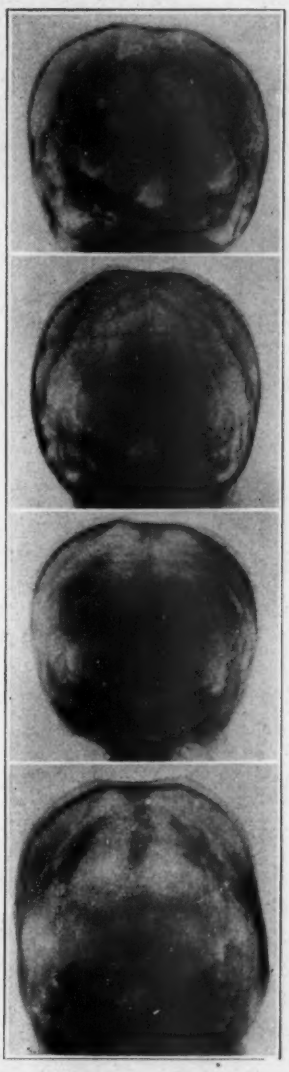

Fig. 2.—Anteroposterior views of the skulls of the three daughters and the father, showing the sagittal furrow which, with the defective clavicles, accounts for the name "cleidocranial dysostosis." The depression seems to be due to stress and strain on the bony membranes, as bone is formed slowly and the usual support is lacking. Note that the lambdoidal sutures are unusually wide in the younger children but closed in the father. All of these changes are well developed at birth.

irregular positions complicated by the presence of many supernumerary tooth buds in the region of the upper and lower incisors and the bicuspids. It is notable that the enamel crown portions of the teeth were normally formed while the roots, or dentinal portions, gave evidence of little or no formation; the root portions of the few teeth that did erupt were markedly constricted.

Fig. 3.—Lateral views of the bones of the face and skull of the three daughters and the father. The crowns of the erupted permanent teeth are normal in formation and structure, but the root portions are notably constricted and cone shaped. There are many supernumerary tooth buds in the lower bicuspid region and in the upper and lower incisor regions. There seems to be no order of eruption of the permanent teeth that are in place. Complete or partial eruption may have extended over thirty years. The deciduous dentition appears to have been normal in formation and time of eruption. Failure of deciduous roots to absorb and excessive wear of the crown are notable.

Fig. 4.—Roentgenograms of the three daughters and the father and of 2 normal controls. Parts of the pelvis developed from different centers of ossification are slow to unite. Note the absence of ossification at the symphysis in all three daughters. Also note the wide epiphysial lines of the femurs in the youngest child and the blunting of the head and shortening of the neck in older members of the family. These changes have not been described previously. The smaller adjacent roentgenograms show normal pelves of children of the same ages (5 and 14 years, respectively).

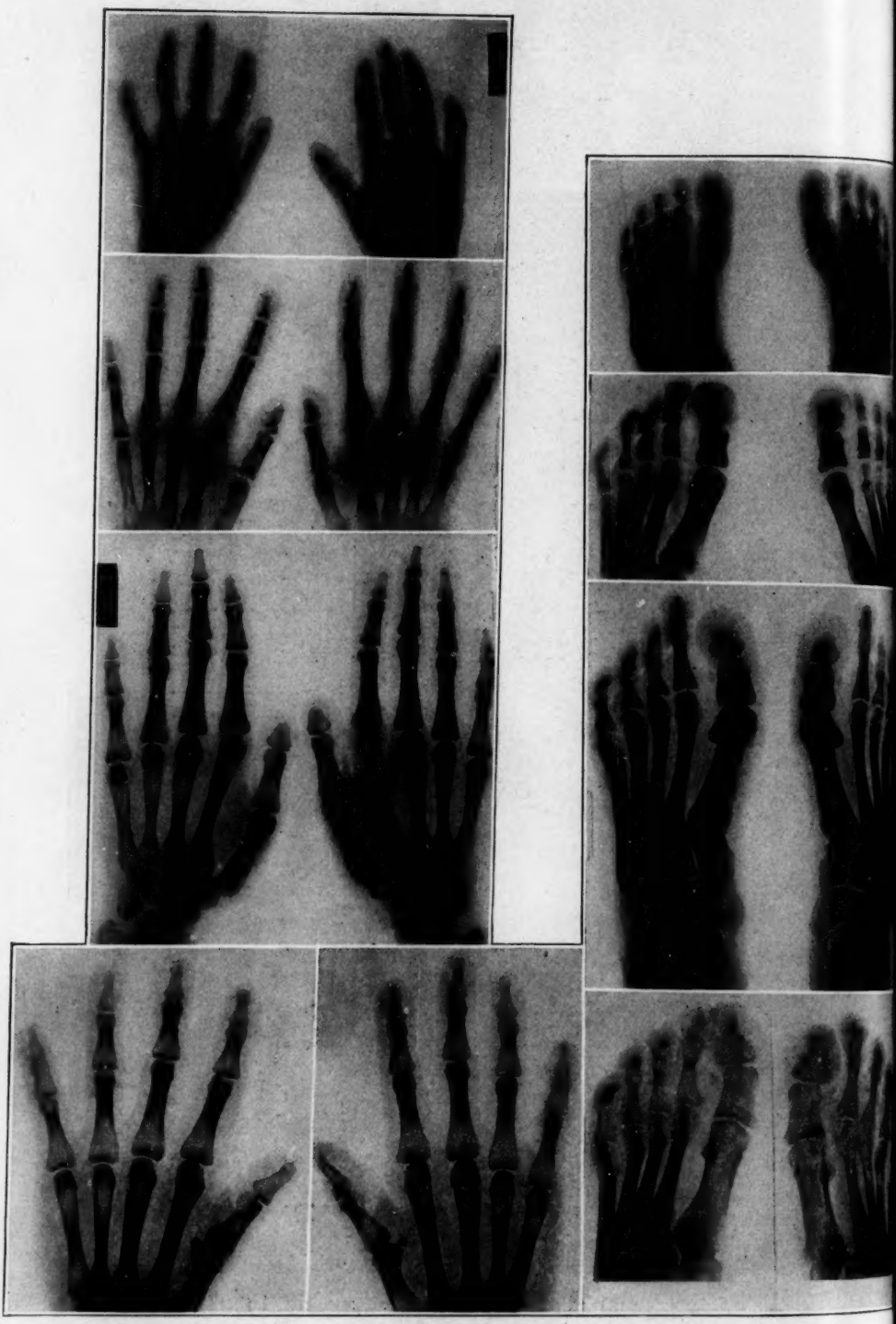

Fig. 5.—Roentgenograms showing fingers and toes of the three daughters and the father. The is absence of the bony flange and shortening of the distal phalanges, especially of the thumbs a great toes. The epiphysial lines are wide and close late. Elongation of the second metatarsal a the metacarpal bone sometimes occurs (Elaine).

Fig. 6.—The father, John, and the three daughters, Patsy, Vivian and Elaine. The shoulders can be approximated anteriorly because of the absence of clavicles. The thumbs are short and the fingers tapered. Note the similarity of facial expressions in this group and the contrast to the normally developed brother and sister (fig. 7).

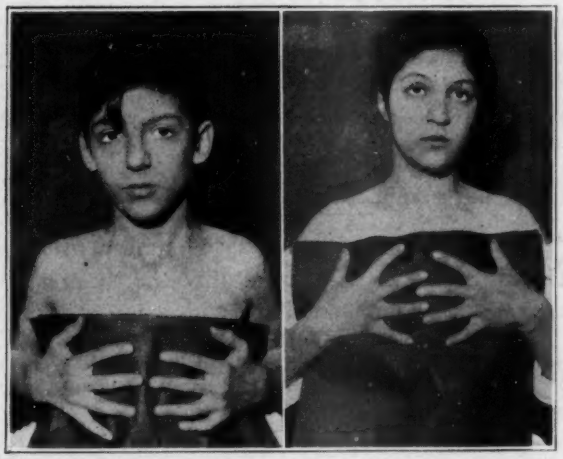

Fig. 7.—Thomas and Sylvia, the normally developed brother and sister. Each has fingers of normal length, wide shoulders and absence of the midline furrow of the forehead. Two other children not shown here are normal. All of the uninvolved members of the family were tall; the involved members were short.

The father, at the age of 61, still had many unerupted teeth, despite the wearing of a dental plate for thirty years.

In the paternal grandmother a tooth erupted at the age of 84, but nothing definite is known about other skeletal changes.

Examinations of the blood showed normal values for calcium, phosphorus and phosphatase. The urine was normal. Neurologic and other tests revealed no defects.

SKELETAL CHANGES IN SUBJECTS WITH DEFECTIVE CLAVICLES

I. Delayed transition of preosseous tissue to bone

1. Partial or complete absence of clavicles (cartilage and membrane)
2. Markedly delayed ossification of symphysis pubis (cartilage and membrane?)
3. Delayed longitudinal growth, with ultimate shortening of long bones (cartilage); mild rickets-like alteration in contour of bones; shortening of stature due presumably to decrease of longitudinal growth, most marked in weight-bearing thigh and leg bones and less marked in arm bones; foreshortening and abbreviation of distal phalanges of fingers and toes, especially of thumbs and great toes.
4. Secondary changes due to an altered rate of transition of membrane and cartilage to bone
   (*a*) Sunken and widened sutures of skull, brachiocephalic skull, pentagonal skull; face small in proportion to size of skull; prognathism; sutures gaping widely at birth and remaining open over the normal period; delayed union of epiphysis
   (*b*) Tendency toward scoliosis, coxa magna, coxa vara, genu valgum and rickets-like flaring at ends of shafts; also tendency toward shortening of weight-bearing bones
   (*c*) Rarely increase (relative) in longitudinal growth with associated mild deformity (second metacarpal and metatarsal bones most often involved)

II. Delayed and defective dentition

1. Marked delay in loss of deciduous teeth (teeth retained beyond the age of 30 years in 1 case)
2. Marked delay in eruption of permanent teeth, which have faulty implantation and frequent impaction (eruption occurring as late as the age of 84)
3. Marked deficiency of development of root portions of all permanent teeth, both erupted and unerupted

COMMENT

Fitchet[4] in 1929 summarized a large number of reports (136) dealing with this subject. He stated that there are two classes of cleidocranial dysostosis, the hereditary and the sporadic. Mendelian characteristics have long been mentioned in connection with the defects of the clavicles and skull. The thought comes to us that sporadic

involvement, in fact, may be hereditary but the condition is so strongly a recessive characteristic that only rarely is it capable of making its appearance in more than one generation.

Theories of origin have implicated "retraction of the amnion with hypertension of the amniotic fluid," [5] rickets, syphilis and an inflammatory process of the brain at birth. That these are totally inadequate to explain the pathogenesis of this combination of malformations seems evident. Steindler [6] stated the belief that "it may be placed in the class of systemic intrinsic deformities, the cause of which lies in early developmental aberration reaching back into the first weeks of embryonic life." In our opinion, this is as far as one can go until more is known about the potential factors governing embryonic development.

A large number of cases of sporadic cleidocranial dysostosis without a hereditary history have been reported. This varies in no special way from the condition recognized in families and transmitted. The changes in the clavicles and skulls have been constantly noted. Fitzwilliams [7] has gone into detail to explain that it is bone formed in membrane that is involved. The decreased longitudinal growth of bones, shown by the short stature observed in the majority of cases, indicates that bone formed in cartilage may be affected. It is possible that a microscopic study would reveal changes at many, if not all, points of transition from cartilage as well as from membrane to bone during the period of active growth. There is definitely a longer preosseous stage than normal. While all parts of the skeleton may reveal this to a slight degree, individual bones are not always similarly affected, and only those showing the greatest change are readily recognizable on roentgenograms. Many "anomalies" associated with the disease are apparently expressions of this deficient growth.

A more or less orderly but slow transition from cartilage to bone occurs in certain other conditions during early postnatal life, but later there is evident a varying degree of change at the junction of cartilage and bone, recognizable at more or less definite periods as a type of dystrophy. Achondroplastic dwarfism and Morquio's disease [8] stand out among conditions of this type. The achondroplastic dwarf and often the normally proportioned dwarf show characteristic changes within a few months after birth. Morquio's disease shows early defi-

5. Jansen, M.: La disostosi cleidocranica, Arch. di ortop. **35**:270, 1919; Dysostosis Cleido-Cranialis, J. Orthop. Surg. **3**:468, 1921.

6. Steindler, A.: Diseases and Deformities of the Spine and Thorax, St. Louis, C. V. Mosby Company, 1929.

7. Fitzwilliams, D. C. L.: Hereditary Cranio-Cleido-Dysostosis, Lancet **2**: 1466, 1910.

8. Meyer, H., and Brennemann, J.: A Rare Osseous Dystrophy (Morquio), Am. J. Dis. Child. **43**:123 (Jan.) 1932.

cient growth and osteocartilaginous changes. Metaphysial segmentation occurs usually about the time of weight bearing, but the skull is always normal. Cleidocranial dysostosis is evident at birth because of the defective clavicles and the median furrow in the skull, but defects of cartilage and membrane elsewhere are not recognized until much later and then often are revealed only as mild rickets-like changes in the bones. The usual type of cleidal involvement is sufficiently different to cause no serious diagnostic problem, but these conditions all have a common trend; that is, bone is formed at a decreased rate.

A suggested relation to a type of achondroplasia was offered by Abram.[9] He described a boy 16 years old, 4 feet and ½ inch (123 cm.) in height and weighing 64 pounds (29 Kg.), who was definitely a dwarf of the achondroplastic rather than of the diminutive, normally proportioned type. This patient had complete absence of the bony tissues of both clavicles and a brachiocephalic skull, defects typical of cleidocranial dysostosis. In this instance there was no evidence of heredity; the mother and father, three brothers and one sister all had normal clavicles. Although this case is the only one of its kind we have been able to find recorded, it seems to connect cleidal dysostosis with an unmistakably achondroplastic condition.

Rickets-like deformities, which were present to a mild extent in many cases, with an occasional wedge-shaped vertebra, scoliosis and coxa magna, emphasize the unstable character of skeletal development which is brought about by an inherently defective growth mechanism. The same tendency to minor "spot changes" outside of the main syndrome is present, but to a lesser extent than in most other cartilage-bone dystrophies. The late osseous changes are relatively mild, and the bone formed is apparently of normal quality.

In two reports[10] cleidal families with defective clavicles were said to have a tendency to be tall, not short, as nearly all have been. These had marked genu valgum. One patient required bilateral osteotomies to correct the deformity. Genu valgum in a varying degree has been a frequent finding in all cases, but it is less pronounced in patients of short stature. At first thought these two families might be considered as ruling against a deficiency in longitudinal growth, which we believe is an almost constant finding of cleidocranial dysostosis. Slight relative elongation of the second metacarpal and metatarsal bones are typical examples of overgrowth and have been noted fairly frequently. The tall patients seem to present an outcropping of a similar change in other long bones, notably the femurs. Increased longitudinal growth in isolated parts of the body has occurred in about the same frequency as other local changes usually referred to as anomalies.

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9. Abram, J. H.: Cleido-Cranial Dysostosis, Lancet **2**:429, 1907.

10. Nettesheim, W.: Ueber Dysostosis cleido-cranialis (Cleidocranial dysostosis), Monatschr. f. Geburtsh. u. Gynäk. **72**:159, 1926. Fitchet.[4]

The zone of proliferating cartilage gives way more readily than normal to forces applied to it, and this seems to account for many of the changes. The cartilage at any one location is subject to slight unequality in growth dependent on these forces. In the end there is flaring of the ends of the shafts of the long bones, in previous descriptions often referred to as rickets. The epiphysial lines and sutures which remain open beyond the usual period indicate delay in the transition from tissues less able to support weight to functionally normal weight-supporting bone. A parallel process is evident in the formation of the teeth. The root portions of the permanent teeth are defective, but the enamel portions, once formed, are apparently normal. We believe that less resistant cartilage and defective dentition are as much a part of the syndrome as defective membrane. The condition is definitely one in which an entirely normal mechanism for developing bone and enamel from preosseous and dentinal tissue, respectively, is lacking.

We have no explanation for the selective effect on the clavicles. It seems that skeletal membrane and cartilage, both of which make up this bone, were not able to develop properly in embryonic life. Later, as in many other bones, postnatal growth proceeded at a decreased rate. It is unique that the clavicle, the first bone formed (sixth week) in embryonic life, and the dental follicles,[10a] formed slightly later (eighth week), should be so markedly affected. The symphysis pubis, the exact origin (membrane or cartilage) of which is in doubt, has not been missing or ultimately grossly defective, but it showed more evidence of delayed ossification in our group than any other bone except the clavicle.

The changes in the shape and contour of the skull, as well as changes in bony contour elsewhere in the body, seem to be partially the result of the pull of natural forces on defective proliferative cartilage and preosseous membrane. Some of these changes are well established at birth; others appear to be due to the stress and strain brought on by locomotion. Resistance to change is progressively increased from the onset in early embryonic life.

Fitchet [4] terminated a splendid review of the cases previously reported with this statement: "It would simplify much of the mass of contradictory evidence if . . . the designation 'hereditary cleidocranial dysostosis' were discontinued, and the condition recognized for what it is, a congenital cleidal dysostosis, either hereditary or nonhereditary, with or without other anomalies." It seems that the associated changes in the skeletal system in these cases are present too frequently to be mere associated "anomalies." One must correlate the slow and somewhat imperfect transition from membrane and cartilage to bone, as well as the defective dentition, with the same process

10a. Heupel, R. G.: Cleidocranial Dysostosis, J. Dent. Research **15**:186, 1935.

that omits all or portions of the clavicles. The lack of dominant mendelian characteristics probably accounts for the infrequency, the slight variation in distribution and degree of the individual changes and the rapid elimination of the whole condition by cross breeding.

In most instances the condition has been sporadic; transfer to two or three generations by either parent has been rare. However, heredity must be considered as a possibility in all cases. Until there is found the cause of the early aberration in embryonic life which impairs preosseous and dental tissues, all of the changes commonly recognizable should be considered a part of the syndrome. The changes in the whole skeleton must be taken into consideration, not just the defects in the skull and clavicles, as in previous reports. The names cleidocranial dysostosis, the original designation, and cleidal dysostosis, used recently by Baer,[11] are useful in that they attract attention to this unusual condition. In our opinion neither gives ample implication of the basic changes in preosseous and dentinal tissue.

SUMMARY

A father and three daughters of a family with nine members had defectively developed or missing clavicles. All four were short of stature; all had prominent frontal eminences and parietal bosses, median furrows of the skull, markedly defective dentition of a special type and abbreviated distal phalanges, especially of the thumbs and great toes. The children showed wide sutures and epiphysial lines, with marked delay in time of closure and mild rickets-like changes in the bones. This family is presented as an example of hereditary defects the cause of which is a defective growth mechanism starting early in embryonic life and asserting itself throughout life. Emphasis is placed on the presence of defective cartilage throughout a large portion of the skeleton. Changes in the ossification of the pelvic bones are shown for the first time. The changes in the skull and clavicles attract attention to the disease, but other associated changes should be included as a part of the syndrome.

11. Baer, R. W.: Congenital Cleidal Dysostosis, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 4, chap. 27.

SEQUENCE OF ROENTGEN EVIDENCE OF TUBERCULOSIS AND CUTANEOUS SENSITIVITY TO TUBERCULIN

A STUDY OF INFANTS

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The chronologic relation between the appearance of a positive reaction to the tuberculin test and roentgen evidence of the childhood type of pulmonary tuberculosis has not as yet been subjected to careful clinical investigation.

The general impression obtained from the majority of textbooks and treatises on tuberculosis is that the positive cutaneous reaction coincides with or antedates roentgenographically recognizable evidence of the primary tuberculous infiltration of lung tissue. If this impression is correct, the logical inference is that cutaneous allergy to tuberculin has already become manifest or is coincidental with the time when the primary pulmonary infiltration has attained sufficient magnitude to be identified by means of the roentgenogram.

During a study of infants exposed to tuberculosis [1] an opportunity was presented to follow these children with roentgen examinations and tuberculin tests before, during and after the development of the primary complex of tuberculosis.

SUBJECTS

The children were referred to the Bureau of Laboratories from various tuberculosis clinics and hospitals in the city of New York. They were all exposed to

From the Bureau of Laboratories, New York City Department of Health, the New York Hospital and the Department of Pediatrics, Cornell University Medical College.

1. This study has been carried on since 1926 under the auspices of the Bureau of Laboratories, New York City Department of Health. The observations reported in the present paper were collected in the course of an intensive study of the efficacy of BCG and of dead tubercle bacillus vaccine in immunization against tuberculosis initiated under the direction of Dr. William H. Park and Dr. C. Kereszturi. Children who received the BCG vaccine or the dead tubercle bacillus vaccine were eliminated from this study, with the exception of 2 patients whose pulmonary lesions were visible on roentgenograms made before vaccination.

open tuberculosis during the first year of life and were placed under observation before they were 12 months of age. They were studied until they had passed their fifth birthday.

METHODS

These children were followed closely, receiving monthly home visits by the nurses, frequent physical examinations and, wherever possible, roentgen examinations and tuberculin tests routinely at three to six month intervals throughout the period of study.

The tests were performed by one of the staff pediatricians with freshly diluted old tuberculin furnished by the New York City Department of Health. The routine dose was 0.1 mg. of tuberculin given intradermally, but the dose was raised to as much as 10 mg. in certain instances.

The reactions were read and measured at the end of forty-eight hours by specially trained nurses, recordings being made in millimeters of the areas of redness and infiltration. For the purpose of this paper the reactions are charted according to the standards suggested by the National Tuberculosis Association.[2]

The question may be raised whether a routine dose of tuberculin in excess of 0.1 mg. might not have been preferable to the dose used in this study. It is likely that a higher dose might have resulted in a few additional positive reactions, but the percentage of error due to the size of the dose is probably small. Barnwell and Pollard[3] found in a study of 212 children with positive tuberculin reactions that 96 per cent reacted to 0.1 mg. of tuberculin or less, the remaining 4 per cent reacting only to a dose of 1 mg. Hart[4] in a study of 1,030 clinically tuberculous patients found that 96.3 per cent reacted to 0.1 mg. of tuberculin given intradermally. Of the 38 who reacted negatively to 0.1 mg., 10 showed a positive reaction to 1 mg. (an addition of only 0.9 per cent), and the reactions of only 4 more became positive with the application of 10 mg. of tuberculin (5 were not tested with this concentration). Nineteen children persistently gave negative reactions with the larger dose.

Of the 16 children reported on in our study, 5 gave a negative response to doses of tuberculin varying from 1 to 10 mg.

The roentgenograms were originally read as soon as they were taken. At the completion of the study they were again reviewed in serial form without knowledge of the results of the chronologically corresponding tuberculin tests. This procedure permitted interpretation of the films in retrospect and without bias.[5]

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2. According to these standards, 1 plus indicates an area of edema less than 10 mm. in diameter; 2 plus, an area 10 to 15 mm. in diameter raised more than 1 mm. above the surface of the skin; 3 plus, an area more than 15 mm. in diameter raised more than 2 mm., with diffuse redness but no necrosis, and 4 plus, extensive edema, redness and necrosis (Chadwick, H. D., and McPhedran, F. M.: Childhood Type of Tuberculosis, New York, National Tuberculosis Association, 1931).

3. Barnwell, J. B., and Pollard, H. M.: Am. Rev. Tuberc. **30**:482, 1934.

4. Hart, P. D.: The Value of Tuberculin Tests in Man, with Special Reference to the Intracutaneous Test, Medical Research Council, Special Report Series, no. 164, London, His Majesty's Stationery Office, 1932.

5. Roentgenograms were initially read by the departments of roentgenology of the hospitals at which they were taken, then by myself and finally by Dr. John R. Carty, director of radiology at New York Hospital and associate professor of roentgenology, Cornell University Medical College.

The following criteria were accepted as indicating the presence of pulmonary infiltration of the primary (childhood) type of tuberculosis: pulmonary infiltration of a chronic nature, enlargement of the adjacent lymph nodes and terminal calcification of the pulmonary infiltration, of the regional lymph nodes or of both. The latter rigid criterion excluded a number of cases in which the condition was presumably of tuberculous origin but terminated in complete resolution of the primary complex without evident deposition of calcium.

RESULTS

In this study of over 2,000 infants from tuberculous homes in New York, the complete evolution of the primary complex of tuberculosis, from early pulmonary infiltration to calcification or death, was observed in 63 children.

A careful study of these 63 infants demonstrated that parenchymal involvement of lung tissue, as shown by roentgen examination, preceded the development of a positive tuberculin reaction in 16 instances.

It is impossible to state whether this sequence occurred in the remaining cases, since 35 of the children had both a positive pulmonary roentgenogram and a positive tuberculin reaction when first observed, and the remaining 12 children were inadequately studied in terms of roentgen examinations and cutaneous tests.

It is of interest that, as shown in the final tabulation, in none of the 63 cases was the tuberculin reaction positive and the roentgenogram unequivocally negative at the outset, although a number of the roentgenograms were initially read as doubtful or negative.

Table 1 and figure 1 present a summary of the cases in which there was roentgen evidence of pulmonary tuberculous infiltration prior to the development of a positive cutaneous reaction. Tables 2, 3 and 4, which give further data on the tuberculin tests and roentgen examinations of 3 patients, reveal more clearly the relative times of the parenchymal infiltrations and the positive cutaneous reactions.

It is to be noted that all of the children were followed in early infancy, 11 of the 16 receiving their first tuberculin test while still under 4 months of age, whereas all received roentgen examinations and tuberculin tests before they reached the age of 9 months.

The evolution of a negative to a positive tuberculin reaction occurred before the end of the second year in all cases. This development did not appear to be hastened by the frequency with which tuberculin tests were performed nor by an increase in the dosage. In 1 case (A. K.) 22 tuberculin tests were given within seven months before the first

TABLE 1.—*Interval Between Time of First Positive Roentgenogram and First Positive Tuberculin Reaction*

Patient	Date of Birth	Date of First Negative Tuberculin Reaction	Date of First Positive* Roentgenogram	Date of First Positive† Tuberculin Reaction	
W. D.	1/29/30	5/ 8/30‡	5/19/30	8/13/30	Tuberculosis of knee developed
M. G.	3/14/31	6/28/31	10/ 1/31	1/28/32	
A. B.	1/12/32	8/ 2/32	8/ 9/32	9/12/33	
R. K.	1/26/32	5/19/32	7/ 7/32	5/11/33	
N. G.	10/21/32	4/20/33	4/20/33	6/21/34	
C. B.	4/15/33	11/23/33§	12/ 7/33	1/11/34	BCG vaccine given 12/14/33
S. G.	5/ 5/33	8/24/33	8/24/33	3/ 8/34	
A. K.	10/ 7/33	10/25/33‡	2/ 8/34	4/12/34	Died 1/19/35 with miliary tuberculosis
N. O.	8/24/34	3/21/35	3/22/35	5/ 3/35	
M. D.	2/ 9/35	3/12/35	7/20/35	1/12/37	Died 2/26/37 with miliary tuberculosis
C. D.	6/ 2/35	8/16/35	8/13/35	2/17/37	
J. P.	6/11/35	3/ 5/36	4/11/36	4/21/36	BCG vaccine given 3/18/36; died 8/25/36 with miliary tuberculosis
A. T.	8/ 1/35	9/17/35	9/26/35	7/ 9/36	
J. H.	9/ 7/35	10/ 6/35	10/11/35	12/ 5/35	
G. V.	1/17/36	4/ 9/36	4/ 9/36	3/18/37	
E. W.	6/10/36	9/21/36	10/ 2/36	6/19/37	

† Three to 8 tuberculin tests were given between the first negative and the first positive reaction. A. K. received 21 tests in this interval.

* Five to 13 roentgen examinations were made between the time of pulmonary infiltration and mediastinal enlargement and the time of calcification.

‡ Negative up to 10 mg.

§ Negative up to 2 mg.

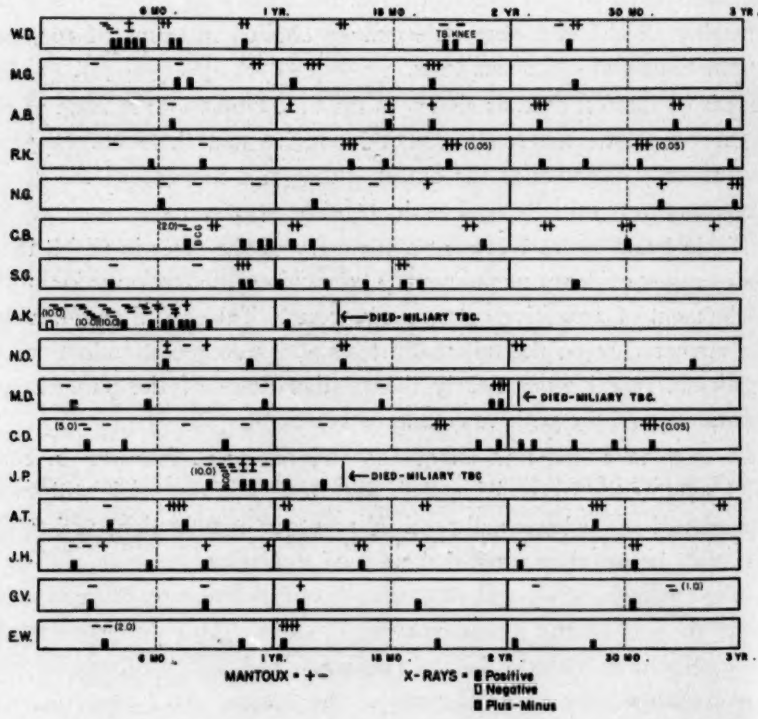

Fig. 1.—Chart showing the relative times when roentgenograms and tuberculin tests were made during the first three years of the study.

TABLE 2.—*Relation Between Tuberculin Reactions and Roentgen Findings in the Case of W. D.**

Date	Tuberculin Tests: Dose, Mg.	Tuberculin Tests: Reaction	Roentgen Findings
5/ 8/30	0.1	Negative	
5/13/30	2.0	Negative	
5/19/30			Massive infiltration upper lobe of left lung
5/20/30	10.0	Negative	
5/27/30	10.0	Negative	
5/28/30			Massive infiltration upper lobe of left lung
6/ 8/30	0.2	5 mm. area of redness and infiltration	
6/16/30			Infiltration condensed to area near left hilus
6/27/30			Infiltration near left hilus
8/13/30	0.1	15 mm. area of infiltration, 20 mm. area of redness	Infiltration near left hilus
8/28/30			Pulmonary fields clearer; slight infiltration of lower lobe of left lung off left cardiac border
12/ 4/30	0.1	15 mm. area of redness and infiltration	Definite infiltration of lower lobe of left lung off left cardiac border
5/21/31	0.2	15 mm. area of redness, 12 mm. area of infiltration	
10/22/31	0.2	Negative	Marked calcification in left hilus
10/29/31	0.2	Negative	Marked calcification in left hilus
4/ 7/32	0.2	Negative	
4/18/32	0.1	12 mm. area of redness and infiltration	
4/20/32			Calcification as before and calcified area behind left lower cardiac margin

* The infant, born Jan. 29, 1930, was exposed to sputum containing tubercle bacilli from birth to the age of 3½ months. Tuberculosis of the knee was evident on Oct. 22, 1931.

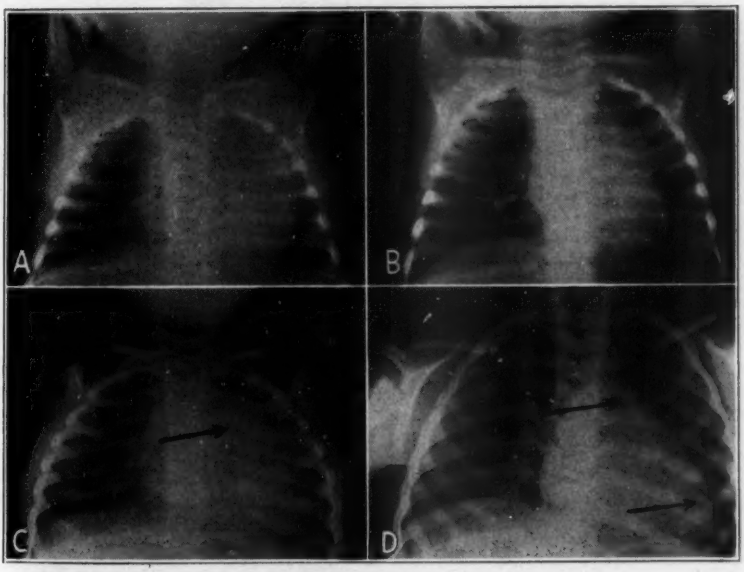

Fig. 2.—Roentgenograms of W. D. *A*, taken on May 19, 1930, at the age of 4½ months, shows massive infiltration in the upper lobe of the left lung. *B* was taken on June 16, 1930, at the age of 5½ months. Infiltration has condensed to an area near the left hilus. *C* was taken on Oct. 29, 1931, at the age of 21 months. Marked calcification is visible in the left hilus and secondary infiltration near the left lower cardiac border. *D* was taken on April 20, 1932, at the age of 27 months. Calcification is marked in the left hilus; a calcified spot is also seen behind the left lower part of the cardiac shadow.

TABLE 3.—*Relation Between Tuberculin Reactions and Roentgen Findings in the Case of E. W.**

Date	Tuberculin Tests		Roentgen Findings
	Dose, Mg.	Reaction	
9/21/36	0.1	Negative	
10/ 2/36	2.0	Negative	Moderately dense shadow near left hilar region; increased right hilar markings
4/15/37			Consolidation of upper lobe of left lung
6/23/37	0.1	++++	Marked consolidation of upper lobe of left lung, with large calcified mass forming in left hilus; early calcification in right hilus
3/ 2/38			Definite calcified masses in upper lobe of left lung and in lower lobe and hilus of right lung; upper lobe of left lung still cloudy
6/30/38			Same as on 3/2/38
10/19/38			Same as on 3/2/38

* The infant, born on June 10, 1936, was exposed to sputum containing tubercle bacilli from birth to the age of 3 months.

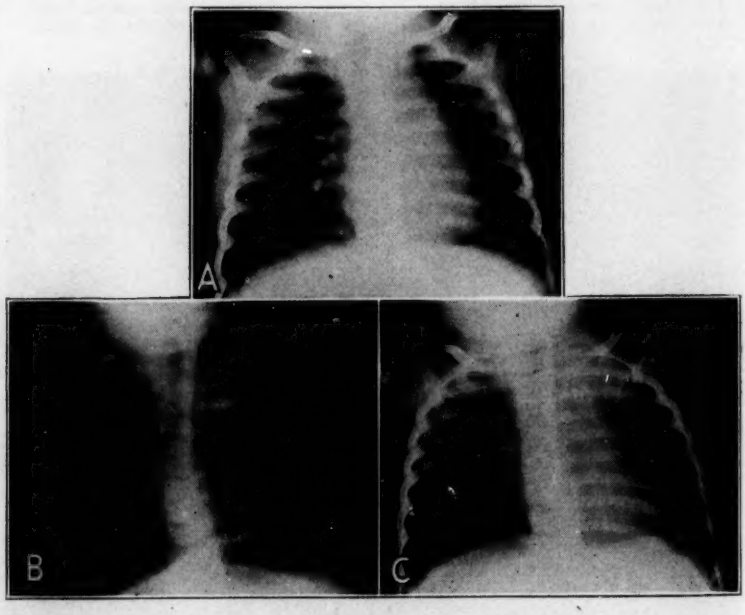

Fig. 3.—Roentgenograms of E. W. *A*, taken on Oct. 2, 1936, at the age of 3½ months, shows a moderately dense shadow near the upper hilar region on the left. There are increased hilar markings on the right. *B* was taken on April 15, 1937, at the age of 10 months. There is consolidation in the upper lobe of the left lung. *C* was taken on June 23, 1937, at the age of 12½ months. Consolidation is still present in the upper lobe of the left lung, with a large calcified mass in the hilus.

positive reaction was obtained. In this instance the first positive reaction was observed nine weeks after the appearance of roentgen evidence of pulmonary infiltration.

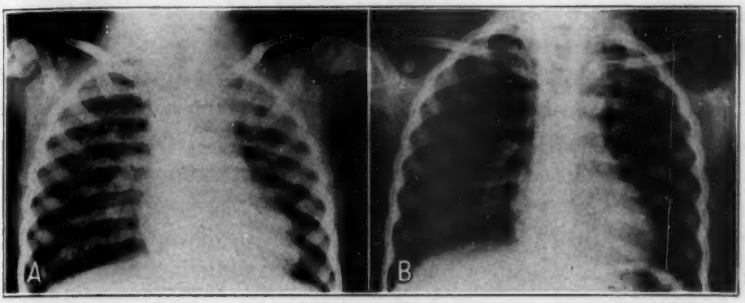

Fig. 4.—Roentgenograms of E. W. *A*, taken on March 2, 1938, at the age of 20¾ months, shows definite calcified masses in the upper lobe and hilus of the left lung and in the lower lobe and hilus of the right lung. *B* was taken on Oct. 19, 1938, at the age of 26 months. Calcification is marked in the upper lobe and hilus of the left lung and in the hilus of the right.

TABLE 4.—*Relation Between Tuberculin Reactions and Roentgen Findings in the Case of M. D.**

Date	Tuberculin Tests		Roentgen Findings
	Dose, Mg.	Reaction	
3/12/35	0.1	Negative	
4/ 2/35			Mottled shadow at eighth spine to right of cardiac shadow; enlarged mediastinum
5/14/35	0.1	Negative	
7/20/35			Definite mottling in lower lobe of right lung; upper lobe of right lung suggestive
7/29/35	0.1	Negative	
1/14/36	0.1	Negative	Calcium deposit at point of lesion in lower lobe of right lung; calcification in upper lobe of left lung opposite fourth spine; mottling throughout right side and upper half of left
7/26/36	0.1	Negative	Poor plate
1/12/37	0.1	40 mm. area of redness and infiltration	Mottling more pronounced throughout right side
2/ 2/37			Fine dissemination throughout right lung

* The infant, born on Feb. 9, 1935, was exposed to sputum containing tubercle bacilli from the age of 2 months to the age of 3 months and from 6½ to 22 months. Death occurred on Feb. 26, 1937.

COMMENT

It has been asserted that the primary focus per se, or the initial site of the localization of inhaled tubercle bacilli in the lungs, is generally too small to be visible by roentgenogram and that the pulmonary infiltration surrounding the primary focus is an allergic manifestation which appears only after the body tissues have become sensitized to tuberculin. Such statements appear in many textbooks and articles.

Wallgren [6] stated that "the end of the period of incubation is marked by the appearance of allergy," which asserts itself by a sudden and violent perifocal inflammatory reaction around the tuberculous focus.

Myers [7] expressed agreement with this opinion, stating that "a pneumonic area appears around the focus of tuberculosis when or soon after the tissue becomes sensitized."

The observations presented in this paper demonstrate, however, that in infants a primary pulmonary tuberculous infiltration which is identifiable roentgenographically may precede a positive tuberculin reaction, although cutaneous allergy to tuberculin develops subsequently.

An explanation for these unanticipated results is as yet wanting, but several possibilities suggest themselves, of which the following are the most significant:

1. The primary focus in its preallergic phase may be of sufficient magnitude to be recognized roentgenographically.

2. The pulmonary infiltration may be due to allergy, but the antibodies are held for a time at the zone of the primary focus, their spread to the remainder of the body being temporarily retarded.

3. The pulmonary infiltration is an allergic manifestation which spreads rapidly throughout the entire body, but the slow development of cutaneous sensitivity in certain infants may temporarily delay a positive cutaneous response to the presence of tuberculin.

4. There is relative inability of young animals to form antibodies.

The first possibility receives some support from the work of Rich and McCordock,[8] who demonstrated experimentally that the primary pulmonary infiltration of tuberculosis is not necessarily an allergic response. These authors introduced a saline suspension of tubercle bacilli intratracheally into the lungs of normal guinea pigs. Acute tuberculous pneumonia (polymorphonuclear and mononuclear exudate) followed, with slight early necrosis of the area. The same suspension of bacilli introduced into the lungs of allergic animals called forth precisely the same reaction, but the exudate was more plentiful and reached its height earlier, and necrosis was more pronounced. They concluded that the normal (nonallergic) animal may react to the tubercle bacillus with acute inflammation.

It may be postulated that the pulmonary infiltration observed in these children represented an exudative perifocal inflammation analogous to

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6. Wallgren, A.: Primary Pulmonary Tuberculosis in Childhood, Am. J. Dis. Child. **49**:1105 (May) 1935.

7. Myers, J. A.: Tuberculosis Among Children and Young Adults, Springfield, Ill., Charles C. Thomas, Publisher, 1938.

8. Rich, A. R., and McCordock, H. A.: Bull. Johns Hopkins Hosp. **44**:5, 1929.

the nonallergic acute inflammation demonstrated in animals. It should be pointed out, however, that the massive infiltration and enlarged hilar and mediastinal nodes noted in some of the children prior to the appearance of cutaneous allergy appeared to be a far more intense reaction than the relatively mild process observed in the nonallergic animals of Rich and McCordock. Furthermore, the prolonged interval which elapsed between visible evidence of pulmonary infiltration and the appearance of a positive tuberculin reaction in many of the infants is far beyond the usual duration of the preallergic phase of experimental tuberculosis.

The second concept, that the allergic response of the lung tissue surrounding the primary focus (inciting antigen [9]) may precede and be more severe than the allergic response of the skin to the same antigen injected intradermally, has been studied by several investigators.

Fox [10] concluded on the basis of his experimentation that normal lungs are only slightly permeable to antibodies and that such antibodies are retained in the lungs over a relatively prolonged period. Fox also showed that antibodies tended to localize in areas of inflammation and that the older the inflammatory lesion, the less likely was it to localize antibody.

Cannon and Sullivan [11] found that "the local injection of antigen into previously mobilized histiocytic tissue (of rabbits) may lead to the local formation and retention of immune bodies in relatively high concentration, from which tissue they may diffuse and be recovered in lower concentration in organs elsewhere."

Menkin [12] concluded, on the basis of his experiments, that an acute inflammatory process forms at a site of infection which, through a network of fibrin and occlusion of lymphatic vessels, tends to wall off the area so that foreign substances fail to spread readily from it. He showed that horse serum injected into the circulation accumulates at the site of an acute inflammation, from which it fails to drain away readily. Menkin stated: "It is conceivable in view of the experiments with horse serum that, in a like manner, tuberculo-protein may accumulate from the blood stream in the inflamed tuberculous lesion and, by its presence there, induce an enhanced local inflammatory action."

If the theory of a barrier set up at the site of acute inflammation and limiting the spread of antibodies in animals is applicable to the

9. Although there is still some discussion as to whether or not antibodies develop in the course of a tuberculous infection, it is generally believed that this occurs and that the tuberculin test represents an antigen-antibody reaction.

10. Fox, J. P.: J. Immunol. **31**:7 and 293, 1936.

11. Cannon, P. R., and Sullivan, F. L.: Proc. Soc. Exper. Biol. & Med. **29**: 517, 1932.

12. Menkin, V.: J. Exper. Med. **52**:201, 1930.

primary type of tuberculosis in human beings, it may explain, in part at least, the delayed response of the skin to the injection of tuberculin in the children reported.

Here, again, the long time which intervened between the pulmonary infiltration and the positive cutaneous response of many of the infants militates against acceptance of the explanation for the results of the study reported here.

The experiments of Freund [13] may also be of significance in contributing to an explanation of the results obtained in this study. He demonstrated that the intracutaneous tuberculin reaction may be negative or only slightly positive in young guinea pigs but that these same animals are as sensitive to the toxic action of old tuberculin introduced into the peritoneal cavity as are adult tuberculous guinea pigs who showed a definitely positive reaction to the intradermal tuberculin test. He concluded that systemic hypersensitiveness is actively developed in young guinea pigs at a time when the dermal reaction is slight or negative. If this discrepancy in cutaneous response of young and old animals may be assumed to exist in human beings, the early age of the children in this study (all under 1 year) may have contributed to the relative hyposensitivity of their skins to tuberculin.

That cutaneous reactivity and antibody of the tissues may vary independently has also been suggested by the work of Tschertkow and Belgowskaja,[14] Coca, Russell and Baughman,[15] Valtis,[16] Valtis and Saenz [17] and Lesné and Dreyfus-Sée.[18]

The age factor and its relation to the formation of antibodies have been the subject of numerous studies.[19] The literature on this subject

13. Freund, J.: J. Immunol. **17**:465, 1929.

14. Tschertkow, L., and Belgowskaja, E.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **67**:475, 1930.

15. Coca, A. F.; Russell, E. F., and Baughman, W. J.: J. Immunol. **6**:387, 1921.

16. Valtis, J.: Compt. rend. Soc. de biol. **99**:554, 1928.

17. Valtis, J., and Saenz, A.: Compt. rend. Soc. de biol. **99**:1563, 1928.

18. Lesne, E., and Dreyfus-Sée, G.: Compt. rend. Soc. de biol. **98**:919, 1928.

19. Metchinkoff, E.: Ann. Inst. Pasteur **11**:801, 1897. Halban, J.: Wien. klin. Wchnschr. **13**:545, 1900. Decastello, A., and Sturli, A.: München. med. Wchnschr. **49**:1090, 1902. Langer, J.: Ztschr. f. Heilk. (Abt. f. int. Med.) **24**: 111, 1903. Schenk, F.: Monatschr. f. Geburtsh. **19**:159, 344 and 568, 1904. von Graf, E., and von Zubrzycki, J.: Arch. f. Gynäk. **95**:732, 1912. Happ, W. M.: J. Exper. Med. **31**:313, 1920. von Pirquet, C: Wien. klin. Wchnschr. **20**:1123, 1907. Bondy, O.: ibid. **49**:1704, 1908. Fischl, R.: Arch. f. Kinderh. **71**:6, 1922. Biberstein, H., and Osclinsky, F.: Klin. Wchnschr. **3**:1160, 1924. von Gutfeld, F., and Nassau, E.: Jahrb. f. Kinderh. **112**:135, 1926. Tschertkow, L.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **64**:407, 1929. Selter, H.: ibid. **69**:517, 1931. McKenzie, G. M., and Hangar, F. M.: Proc. Soc. Exper. Biol. & Med. **21**:442,

(Footnote continued on next page)

has been well summarized by Baumgartner.[20] The general conclusion has been that young animals and infants seem less able to respond to antigenic stimulation with formation of antibody than older animals and children and that there is much less antibody in the serums of infants.

The possible influence of age on the results presented in this paper is suggested by the fact that of the 16 patients with roentgen evidence of tuberculosis prior to the development of the positive tuberculin reaction, 11 received their first tuberculin test while still under 4 months of age and all had undergone roentgen examination and tuberculin tests before they reached the age of 9 months. On the other hand, of the 35 children each of whom presented both a positive pulmonary roentgenogram and a positive intradermal reaction when first observed, only 3 received their first tuberculin test before the age of 4 months and only 15 before 9 months.

This theory of reactivity, however, is not applicable in toto to human beings, since not infrequently one finds tuberculous infants less than 6 months of age who exhibit a positive reaction to tuberculin.

The available evidence, therefore, is inadequate to provide a definite explanation of the finding of positive roentgen signs of pulmonary tuberculosis before the development of a positive tuberculin cutaneous reaction, but with the present state of knowledge the following possibilities deserve mention:

1. The pulmonary signs may be a preallergic reaction.

2. Allergy may have developed, but (*a*) antibodies may have been concentrated and held within the area of inflammation; (*b*) infantile skin tissue may be hyposensitive to tuberculin, or (*c*) there may be a general paucity of antibodies in the young infant.

Irrespective of the basic mechanisms involved, it seems evident that if these observations are supported by comparable studies of larger series, certain opinions concerning the tuberculin reaction will require revision, since the cutaneous test is now usually accepted as the most delicate diagnostic means for determining the presence of tubercle bacilli in the body.

1924. Bruening, H.: Arch. f. Kinderh. **82**:6, 1927. Sutter, E.: Dermat. Ztschr. **24**:65, 1917. Baumgartner, L.: J. Immunol. **33**:477, 1937. Schkarin, A. H.: Arch. f. Kinderh. **46**:357, 1907. Moll, L.: Jahrb. f. Kinderh. **68**:1, 1908. Friedberger, E., and Simmel, H.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **19**:460, 1913. Thomsen, O.: Ztschr. f. Kinderh. **26**:213, 1917. Petroff, S. A., and Stewart, F. W.: J. Immunol. **12**:97, 1926. Gross, H.: Zentralbl. f. Bakt. (Abt. 1) **109**: 339, 1928. Nattan-Larrier, L.; Ramon, G., and Grasset, E.: Compt. rend. Acad. d. sc. **183**:458, 1926; Ann. Inst. Pasteur **41**:848, 1927. Halber, E.; Hirszfeld, H., and Mayzner, M.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **53**:391, 1929.

20. Baumgartner, L.: Yale J. Biol. & Med. **6**:403, 1934.

SUMMARY

A study of 63 children who contracted pulmonary tuberculosis while under 1 year of age and who were followed from the earliest evidence of a primary complex to calcification or death from tuberculosis demonstrated that 16 of these children presented roentgen evidence of pulmonary infiltration prior to the development of cutaneous sensitivity to tuberculin. These results are contrary to the general impression now held that a positive tuberculin reaction coincides with or precedes the appearance of recognizable roentgen evidence of the early primary pulmonary complex.

The theories which may be advanced as possible explanations of these results have been briefly considered.

7 East Eighty-Second Street.

IRON DEFICIENCY ANEMIA IN CHILDREN

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AND
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During the past two decades great advances have been made in the knowledge of nutritional anemia and the relation of dietary deficiencies to formation of blood. This progress was stimulated largely by the clinical and experimental work of Whipple and his colleagues,[1] who evaluated the hemoglobin-producing properties of many foods by feeding them to anemic dogs and who also confirmed the value of inorganic iron in regeneration of hemoglobin. The prevalence of iron deficiency anemia both in adults and in children and the rapid cure by the administration of large doses of iron led to the study of the causes of this type of anemia.

In 1928 Ahmann and his associates,[2] in a nutritional survey covering the school children in five counties in Florida, found that approximately 39 per cent of them were anemic. While no particular study was made of the causes of the condition, the authors were of the opinion that iron-deficient diets and infection with hookworm and other parasites were the chief agents.

In regions where hookworm infection is prevalent anemia has been regarded as almost synonymous with hookworm disease, but from time to time certain observations have been made which do not support the opinion that the anemia associated with parasitic infection is due entirely to the infection. Abbott [3] demonstrated that diet was the most important factor in mitigating many of the clinical symptoms of hookworm

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From the Division of Nutrition, Department of Home Economics, University of Florida, Agricultural Experiment Station.

1. Whipple, G. H., and Robscheit-Robbins, F. S.: Blood Regeneration in Severe Anemia: XVI. Optimum Iron Therapy and Salt Effect, Am. J. Physiol. **92**:362, 1930; XVIII. Influence of Liver and Blood Sausage, Veal, Eggs, Chicken and Gelatin, ibid. **92**:388, 1930. Robscheit-Robbins, F. S., and Whipple, G. H.: Blood Regeneration in Severe Anemia: XIX. Influence of Spinach, Cabbage, Onions and Orange Juice, ibid. **92**:400, 1930.

2. Ahmann, C. F.; Abbott, O. D., and Westover, G.: A Nutritional Study of the White School Children in Five Representative Counties of Florida, Bulletin 216, University of Florida, Agricultural Experiment Station, 1930.

3. Abbott, O. D.: The Effect of Improved Diet on Children with a Moderate Degree of Hookworm Infection, J. Home Econ. **26**:577, 1934.

infection. Ashford and his associates [4] concluded from their investigations in Puerto Rico that elimination of the parasites would bring about rapid increase in hemoglobin in the majority of instances; but the observations of Rhoads and his co-workers [5] offer a striking contrast to this conclusion. They found that the removal of the parasites resulted in little improvement of the hemoglobin level. On the other hand, without the removal of the parasites, the mere addition of iron salts to the diet invariably resulted in prompt improvement of the blood values and of the clinical condition.

According to Kracke and Garver,[6] anemia of malnutrition is frequently found in people whose diets are deficient in iron but adequate in other respects. These investigators made blood studies of 312 college women of the Southern states who were apparently in good health and noted that the average hemoglobin value was only 70 per cent (Dare). Further studies were made on more than 100 cotton mill workers. The adults had an average of 4,220,000 red cells per cubic millimeter and 50 per cent hemoglobin, while the children's blood showed essentially the same values. From careful study of the food habits of this group it was evident that the diets were lacking in iron; the daily administration of 30 grains (1.94 Gm.) of iron and ammonium citrates speedily raised the hemoglobin level.

The present report concerns a study of the hemoglobin values of groups of children in Florida and the effect which iron salts or diets high in iron have on regeneration of hemoglobin.

METHODS

A study was made of the hemoglobin values of two groups of children. The first was composed of those in grades 1 to 3 of fourteen rural schools; the second included those in nursery schools (ages 3 to 5 years) whose parents were on relief or working on relief projects. In estimation of the hemoglobin the Dare hemoglobinometer (13.77 Gm. equals 100 per cent) was used. According to present clinical standards hemoglobin values as low as 9.64 Gm. (70 per cent) are considered anemic and those below 11.70 Gm. (85 per cent) subnormal. After these determinations were made, 200 school children (from group 1) with hemoglobin values ranging from 35 to 70 per cent and 47 nursery children (from group 2) with values from 40 to 60 per cent were selected for treatment. Except in a few cases, all came from families in which 2 or more children were anemic. The general treatment for the first group consisted of giving 15 grains (0.97 Gm.) of iron

4. Ashford, B. K.; King, W. W., and Gutiérrez Igaravídez, P.: Report of the Commission for the Study and Treatment of "Anemia" in Porto Rico, San Juan, Porto Rico, Bureau of Printing and Supplies, 1904.

5. Rhoads, C. P.; Castle, W. B.; Payne, G. C., and Lawson, H. A.: Hookworm Anemia: Etiology and Treatment with Special Reference to Iron, Am. J. Hyg. **20**:291, 1934.

6. Kracke, R. R., and Garver, H. E.: Diseases of the Blood and Atlas of Hematology, Philadelphia, J. B. Lippincott Company, 1937, p. 190.

and ammonium citrates orally after each meal. As funds and facilities were available for providing food for selected anemic children of the second group, these were given no iron salts but instead a diet high in iron content. The major part of the food was provided by governmental relief agencies, and the meals were prepared in the school under the supervision of a dietitian. While the diet was perhaps not optimum in all respects, it was considered adequate, since, in addition to the

TABLE 1.—*Grouping of Eight Hundred and Thirty-Three Children According to Hemoglobin Values*

				Hemoglobin Values					
Group	School	No. of Children Examined	Ages, Yr.	12.53-13.77 Gm., 91-100%	11.15-12.39 Gm., 81-90%	9.78-11.02 Gm., 71-80%	8.40-9.64 Gm., 61-70%	7.02-8.26 Gm., 51-60%	2.80-6.88 Gm., 21-50%
1	Rural	620	6-10	12	80	174	173	97	84
2	Nursery	263	3-6	9	61	105	48	24	16
	Total.....	883	....	21	141	279	221	121	100

TABLE 2.—*Effect of Daily Administration of Forty-Five Grains of Iron and Ammonium Citrates on Regeneration of Hemoglobin of Two Hundred Anemic School Children (Group One)*

No. of Cases	Initial Range of Hemoglobin Values		Final Range of Hemoglobin Values After 42 Days	
	Gm.	%	Gm.	%
30	4.82-5.51	35-40	10.33-11.02	75-80
[illegible]	5.65-6.88	41-50	10.74-11.70	78-85
70	7.02-8.26	51-60	11.02-12.12	80-88
60	8.40-9.64	61-70	11.43-12.67	83-92

TABLE 3.—*Effect of Improved Diet on Regeneration of Hemoglobin of Forty-Seven Anemic Nursery School Children (Group Two)*

No. of Cases	Initial Range of Hemoglobin Values		Range of Hemoglobin Values After 30 Days		Range of Hemoglobin Values After 90 Days	
	Gm.	%	Gm.	%	Gm.	%
21	5.64-7.02	41-50	7.57-8.95	55-65	8.26-10.74	60-78
26	7.44-8.95	54-65	9.64-11.84	70-86	10.74-12.11	78-88

food provided at school, the children ate breakfast and supper at home. The schedule for feeding at school included midmorning lunch at 10 a. m., dinner at 12:30 and midafternoon lunch at 3:30 p. m.

RESULTS AND COMMENT

The data presented in table 1 cover the hemoglobin values of 620 rural school and 263 nursery school children. Nearly 50 per cent of all the children were definitely anemic, while 31 per cent had borderline anemia. It is of interest that there are five times as many children in

the groups with the lowest hemoglobin values as in those with the highest. Moreover, many of the lowest values reached a dangerous level.

The effect of iron salts and improved diet on the regeneration of hemoglobin is illustrated in tables 2 and 3. These data show that the administration of iron and ammonium citrates over forty-two days resulted in a rapid increase, or regeneration, of hemoglobin. But it is shown also that while a diet high in iron produced some increase in hemoglobin in all the children, in cases of severe anemia, even after ninety days of the diet, the hemoglobin values remained subnormal.

In this study it was found that the initial blood picture of the nursery school children was in general superior to that of the older group. This is attributed in part to the fact that the former doubtless received better home care in respect to diet than the older children and in part to the fact that the nursery school children had been provided for by local relief agencies.

In the general examination it was found that many of the children did not show alarming symptoms of anemia until the deficiency was fairly severe, often with the hemoglobin reduced as much as 50 per cent. This late manifestation of symptoms was due in part to the fact that the condition was chronic. A number of these children had been born of anemic mothers and probably had been anemic in some degree for the greater part of their lives. Absence from school was caused by such indefinite complaints as listlessness, dizziness, faintness, colds, feeling tired and not feeling well, the majority of which resulted ultimately from an anemic condition. Thus, while many children are able to withstand relatively severe anemia apparently with no symptoms of the condition, the existence of the anemia may be disclosed by symptoms unrecognizable as such by the average observer.

While the general symptoms of anemia differ somewhat according to the individual, the most pronounced are pallor, general muscular weakness and faintness. Of the several symptoms the color and texture of the mucous membranes offer the most reliable external criteria for diagnostic purposes. In severe anemia the mucous membranes of the lips are spongy and yellow, with marked paleness throughout the entire oral cavity.

The most serious and alarming symptom noted was a soft systolic murmur, often associated with tachycardia. This murmur was particularly noticeable during the marked increase in pulse rate occasioned by exercise. After a rest period of two minutes the very slight decrease in heart rate indicated inadequate compensation.

While the general external symptoms give unmistakable evidence of anemia, the blood picture is the only reliable means of determining its degree of severity. Except in the cases in which hookworm infection had produced eosinophilia, the blood examined showed the characteristic

reduction of hemoglobin and of cell size typical of hypochromic anemia. With severe involvement the red cells appeared pale and were of all shapes and sizes; a few were rather large, but the majority were smaller than the normal cell. Other abnormal bodies were observed in the blood. These were almost colorless disks, veil-like in appearance, 40 to 50 microns in diameter, with pink crescents in the margins. These bodies (*corps en demi-lune*) are nonspecific general indicators of anemia. The hemoglobin concentration in the most severely affected patients examined was as low as 25 to 30 per cent. It was found that some children with hemoglobin values even as low as 25 per cent were attending school. Their attendance was of course irregular, but they were a part of the school and were expected to take part in its activities. As their condition was considered to be dangerous, children found to have hemoglobin values of 35 per cent or less were not selected for this report but were placed under proper supervision, hospitalized or put to bed at home.

The administration of iron and ammonium citrates in adequate amounts was found to correct the anemic condition of the children; but diet alone, even after ninety days, did not restore the hemoglobin to normal levels when the initial values were less than 50 per cent. It was observed in many cases that during the administration of iron the hemoglobin increased as much as 2 per cent daily; but as the values approached normal the rate of increase was less. As this treatment continued the usual signs of basophilic degeneration—variation in the size and shape of cells and the central pallor so conspicuous in the stained cell—gradually disappeared.

During the treatment a remarkable improvement in the well-being of the children was noted. One of the first indications was an increase in appetite, which occurred even before there was a gain in hemoglobin. As the hemoglobin values rose there was a marked increase in both mental and physical energy. Frequently it was noted that the severely anemic child was older than the others in the grade: An 11 year old child might remain in the second or third grade, showing no yearly progress. In such cases it was evident that the backwardness in school was due primarily to physical rather than mental inability; for after the hemoglobin reached normal levels many apparently dull, listless children were transformed into normal pupils, participating in the activities of the school with a degree of animation which a month before would have been impossible.

CONCLUSIONS

From the work reported here it is evident that iron deficiency causes an anemic condition in children and that such a condition may be prevented by adequate diet and cured by iron salts. Diets high in

carbohydrates, which are necessitated by poverty, lack of foresight in planning or ignorance of proper buying and of food values, are factors leading to iron deficiency. In individual cases, parasites and gastro-intestinal disturbances resulting from parasitic infection may bring about a chronic deficiency in iron. In this connection it should be mentioned that, in spite of the fact that many children were infected with hookworm, the administration of iron raised the hemoglobin to normal levels and mitigated other symptoms usually associated with hookworm infection. However, the importance of eradicating hookworm and of taking sanitary measures to prevent infection should not be minimized; for if iron is administered after the removal of the parasites, a quicker return to health is assured.

Obviously, in any community where nutritional anemia and hookworm are endemic, the maintenance of children on a high plane of nutrition is imperative. The costly results of failure in this respect are evident.

SUMMARY

A study of hemoglobin values of 883 rural school children in Florida showed that 50 per cent of them were anemic and that 31 per cent had borderline anemia.

The ratio between the number of children with the highest and the number with the lowest hemoglobin values was approximately 1 to 5.

The administration of iron and ammonium citrates to 200 rural school children over forty-two days resulted in a rapid regeneration of hemoglobin.

A diet high in iron-carrying foods produced an increase in hemoglobin in the forty-seven nursery school children; but in cases of severe anemia, even after ninety days of the diet, the hemoglobin values remained subnormal.

Case Reports

DIPHTHERITIC OR STAPHYLOCOCCIC CROUP AND SIMULTANEOUS PNEUMOCOCCIC PNEUMONIA

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It is usually considered desirable to explain associated clinical phenomena as due to a single cause. Consequently when a bacteriologic excitant furnishes a satisfactory explanation for an inflammatory reaction, search for additional bacterial invaders usually ceases. Roentgenographic and physical signs of consolidated lung in the presence of laryngotracheal diphtheria are usually attributed to atelectasis produced by extension of the membrane into terminal bronchioles; further bacteriologic examination is accordingly neglected. The 2 cases reported here exemplify the presence of two separate etiologic agents in a case of infection of the respiratory tract, one causing inflammation of the larynx and trachea and the other inflammation of the lung.

Our first patient had a tonsillar, uvular, laryngotracheal and bronchial diphtheritic membrane, which was removed by suction. In spite of large doses of diphtheria antitoxin, elevation of temperature and rapidity of pulse and respirations persisted. The constitutional reactions and the radio-opacity of the lower part of the left pulmonary field suggested the possibility of additional infection. Two specimens of mucus obtained by swabbing the pharynx were examined. In the second, Pneumococcus type I was observed. An adequate dose of homologous antipneumococcus serum terminated the illness. It is impossible to say whether the two infections were simultaneous in onset or which was the first invader.

The second patient had laryngotracheitis due to Staphylococcus albus, for which intubation and ultimately tracheotomy were performed. Bronchopneumonia due to Pneumococcus type XXIX was noted on the

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This study received financial support from the Littauer Pneumonia Research Fund of New York University College of Medicine, from the Metropolitan Life Insurance Company and from Mr. Bernard M. Baruch, Mr. Bernard M. Baruch Jr., Miss Belle N. Baruch and Mrs. H. Robert Samstag.

fifth day of illness, when the respiratory rate, temperature and pulse rate rose. The patient received homologous specific antipneumococcus serum and recovered.

We have observed several additional cases of pneumococcic infection of the lung associated with staphylococcic or streptococcic infection of the upper airway in which there was favorable response to homologous antipneumococcus serum.

REPORT OF CASES

CASE 1.—*Diphtheritic Group and Type I Pneumococcic Pneumonia.*

A girl aged 5 was admitted to the Willard Parker Hospital on April 24, 1938, at 12:45 p. m. (fig. 1). There had been no previous contagious disease or immuni-

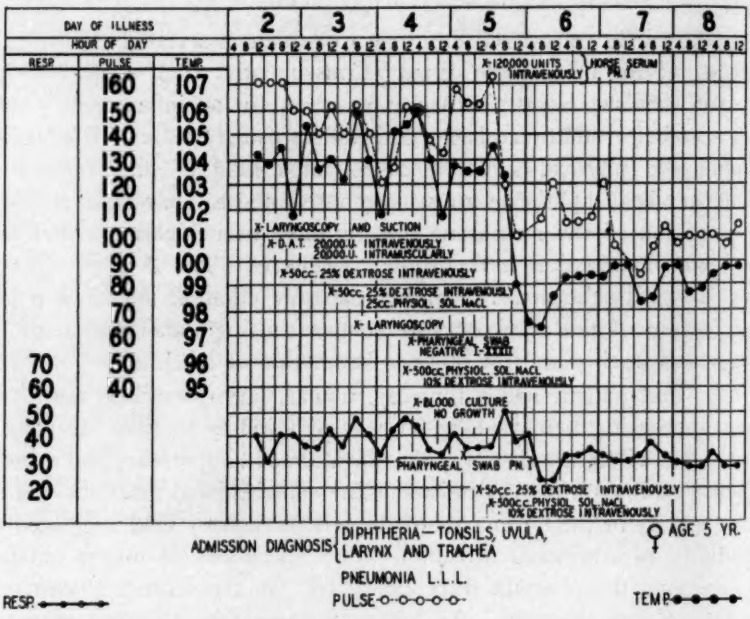

Fig. 1 (case 1).—Chart showing the course of the illness.

zation for diphtheria. The present illness began with a sore throat one day before the child's admission. On the following morning (the day of admission) there was respiratory difficulty, and the temperature rose to 105.6 F. The family physician administered 20,000 units of diphtheria antitoxin, of which 10,000 units was given intravenously.

On the patient's admission the temperature was 104.2 F., the respiratory rate 40 and the pulse rate 160. The child was well developed and well nourished but appeared acutely ill, toxic and extremely pallid. There were no petechiae. There was no nasal membrane or discharge. There was enlargement of the anterior and posterior cervical lymph nodes, which were not tender. A patchy thick white membrane covered the large, moderately injected tonsils and the

uvula. On laryngoscopic study it was seen that the membrane covered the larynx and extended to the trachea. The voice was hoarse and the patient dyspneic. Over the pulmonary fields breath sounds were practically absent except in the apexes of the lungs, where they were diminished. The heart sounds were of poor quality and without murmurs. The membrane was aspirated from the bronchi. The culture showed Klebs-Löffler bacilli.

Forty thousand units of diphtheria antitoxin was given, 20,000 units intravenously. A large amount of membrane was aspirated, with immediate marked benefit. The voice became clearer, and the dyspnea was relieved. On auscultation the breath sounds were still diminished, but they were louder than previously, and the child was apparently getting sufficient air. No operative procedure was

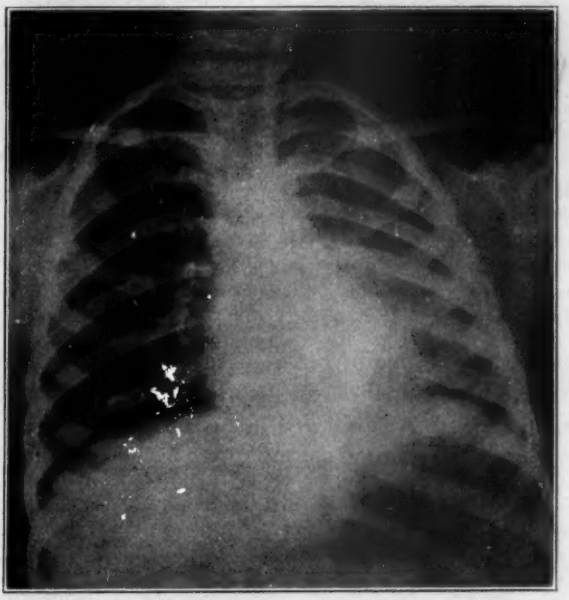

Fig. 2 (case 1).—Roentgenogram of patient with type I pneumococcic pneumonia and laryngotracheal bronchial diphtheria simulating atelectasis.

deemed necessary. The patient was placed in a steam cubicle, and dextrose (50 cc. of a 25 per cent solution) was given intravenously. The child did well until 7:50 p. m. of the same day (April 24), when suction was again applied because of increasing dyspnea and pallor. Again a large amount of thick white membrane was removed, with marked relief.

The following day (April 25) the temperature ranged from 104 to 106 F. Physical examination revealed membrane still present on the uvula and tonsils. Percussion over the lungs revealed no change; the breath sounds were diminished, with scattered coarse rales. There was a croupy cough, and the voice was hoarse. Roentgen examination of the chest showed radio-opacity in the lower lobe of the left lung (fig. 2). The heart was displaced to the side of the lesion; the diaphragm was elevated, and the interspaces were narrowed.

On April 26 the temperature still ranged from 102 to 106 F. There was no respiratory difficulty, but the child was breathing rapidly. The croupy cough and hoarse voice were still present. There was no change in physical findings, and there was no membrane on the tonsils and uvula. The temperature rose to 106.3 F., and the respiratory rate to 42 at 4 p. m.; examination of the lungs at this time revealed dulness over the lower half of the left side of the chest posteriorly with bronchial breathing and fine moist rales. The tentative diagnosis was pneumonia in the lower lobe of the left lung. Typing of sputum obtained by pharyngeal swab was attempted. It was reported that pneumococci were present but that no capsular swelling was demonstrable with 32 types of serum. A blood culture was subsequently reported negative.

On the following morning, April 27 (fifth day of illness), typing of sputum obtained by pharyngeal swab at 9 a. m. revealed Pneumococcus type I. One hundred and twenty thousand units of type I pneumococcus horse serum (Lederle) diluted with 250 cc. of a physiologic solution of sodium chloride containing 10 per cent dextrose was immediately given intravenously. When the serum was administered the temperature was 103.6 F. There was a slight rise to 104.2 F. after injection. The temperature dropped to 99 F. in slightly less than ten hours. Roentgen study at the bedside at this time revealed increase in the size of the radiopaque area.

After serum therapy there was remarkable improvement in the condition of the child. The temperature, pulse rate and respiratory rate remained normal until the tenth day, when mild urticaria and a rise in temperature occurred. The recovery was otherwise uneventful. Roentgen studies on May 2 showed no pleural or pulmonary changes.

In this case no lessening of radio-opacity or improvement in physical signs occurred, in spite of bronchial aspiration and diphtheria antitoxin, but an immediate crisis was induced by an adequate amount of homologous antipneumococcus serum.

CASE 2.—*Staph. Albus Obstructive Laryngitis (Croup) and Type XXIX Pneumococcic Bronchopneumonia.*

A boy aged 8 months was admitted to the Willard Parker Hospital on Aug. 13, 1938 (fig. 3). There had been no immunization to diphtheria. On August 6 the child had diarrhea. On August 9 difficulty in breathing and retraction of the chest developed, and the diarrhea recurred. On the patient's admission there were both retractions and a croupy cough. Laryngoscopic study showed minimal congestion and edema of the larynx with supraglottic edema. The breath sounds were diminished throughout the chest, most markedly on the left side anteriorly. On August 14 (fifth day) the condition became worse; the cords were now dull gray, fleshy, wet and edematous, their condition being characteristic of staphylococcic infection. Intubation with a 9 month O'Dwyer tube produced marked improvement. Cultures of material from the larynx, pharynx and nose yielded Staph. albus.

On August 15 (sixth day), the tube having been coughed up, reintubation was done at 8:15 a. m. There were many coarse rales throughout the chest, but with the tube in place no bronchial breathing could be detected. The temperature, pulse rate and respiratory rate had risen. A roentgenogram (fig. 4) showed moderate mottling of both pulmonary fields. At 11 a. m. there were retractions (3 plus) throughout the chest; the subglottic edema was of 2 plus degree, and reintubation was again done. Retractions continued; they were subcostal, of the

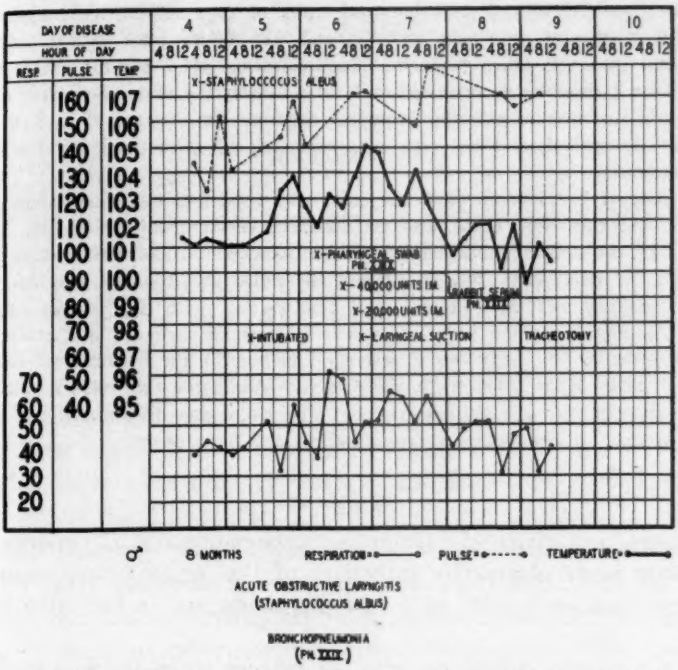

Fig. 3 (case 2).—Chart showing the course of the disease.

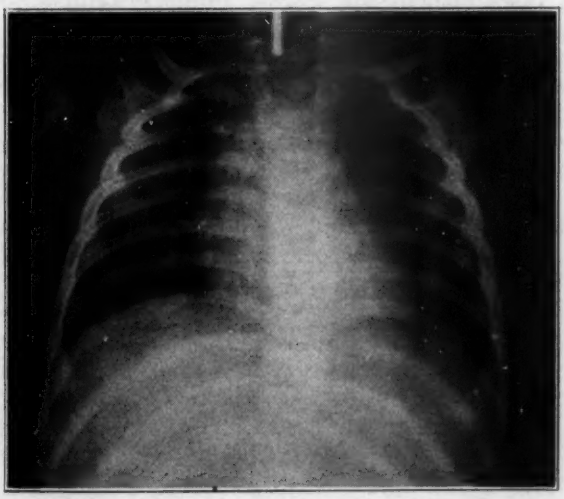

Fig. 4 (case 2).—Roentgenogram of patient with obstructive laryngitis due to Staph. albus and type XXIV pneumococcic bronchopneumonia. The intubation tube is in place.

type usual in pneumonia. Pulmonary secretion obtained from the larynx yielded Pneumococcus XXIX. Forty thousand units of type XXIX antipneumococcus serum was injected into one buttock, and five hours later 20,000 units was introduced into the other buttock. Administration of 4 minims (0.25 cc.) of epinephrine hydrochloride preceded each dose. After the first dose severe dyspnea developed; this was relieved by laryngeal suction. On August 15 at 9:45 p. m. suction was applied, and the tube was replaced, all retractions and restlessness being relieved.

On August 16 (seventh day) the color was good and the breath sounds were normal. At this time there was no apparent result from the serum, but on August 17 the child's condition was much improved. The temperature fell to 100.6 F., the respiratory rate to 42 and the pulse rate to 150. On August 18 trial extubation was unsuccessful, and reintubation with a 9 month tube was done. An ulceration was found on the left arytenoid cartilage, and tracheotomy was performed. On September 2 (twenty-fourth day) the tracheotomy tube was removed, after being blocked for three days. While the tube was in place, the degree of subglottic edema was 2 plus. The child was discharged well with a healed wound on September 4 (twenty-sixth day from onset).

SUMMARY

Reports are given of pneumococcic pneumonia in 2 children with coincident acute obstructive infections of the upper airway caused by different etiologic agents, in 1 case diphtheria and in the other Staph. albus.

Pneumococcic pneumonia may be present when there is extensive diphtheria and may be responsible for some of the terminal pneumonias hitherto ascribed to atelectasis.

In both cases homologous specific antipneumococcus serum acted favorably and may have been life saving.

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MENINGOCOCCIC ENDOCARDITIS AND MYOCARDITIS

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While cases of meningococcic septicemia are common, being reported in large series in the literature, those in which accompanying endocarditis and myocarditis have been proved are uncommon. The literature at the present time contains 17 case reports of endocarditis and 12 of myocarditis caused by the meningococcus. Cardiac involvement of these types has proved rapidly fatal in the majority of cases, while in a smaller number the course has been subacute or chronic. Cases have been reported more frequently during the past ten years, as up to 1927 there were only 11 cases in the literature (Rhoads [1]). The duration of the disease varies from ten days (my case) to eight and one-half months (Gwyn [2]), the average being about six weeks.

An early diagnosis of meningococcic septicemia, with its various lesions, is often not arrived at, owing to the resemblance of the symptoms to those of other, more frequent, conditions. The case to be reported is interesting because of the clinical resemblance of the disease to osteomyelitis; it demonstrates the rapid extension of the infection, which involves the meninges, brain, heart, lungs, kidneys, spleen, liver and skin.

REPORT OF A CASE

E. L., a 13 year old boy, was admitted to Children's Hospital on Feb. 4, 1938, complaining of pain in the right ankle. The mother stated that his illness began seventy-two hours prior to admission, since which time he had remained in bed with pain in the right ankle and knee, headache, sore throat and photophobia. He had eaten little since the onset of the illness, and there was bleeding from the gums. He was seen by a physician on the first day of the illness, and a diagnosis of rheumatic fever was made. His condition rapidly became worse. The boy had had scarlet fever, diphtheria, measles, mumps and whooping cough. The family history revealed nothing of importance.

Physical Examination.—The temperature on admission was 105.4 F.; the pulse rate was 124 and the respiratory rate 36 per minute. The boy was acutely ill and extremely uncooperative. The mouth was dry; the lips were cracked and partly

From the Department of Pathology, Ohio State University, and Children's Hospital.

1. Rhoads, C. P.: Vegetative Endocarditis Due to the Meningococcus, with a Case Report, Am. J. Path. **3**:623 (Nov.) 1927.

2. Gwyn, N. B.: Subacute Meningococcal Endocarditis, Arch. Int. Med. **48**:1110 (Dec.) 1931.

covered with dry blood. The teeth were carious and gums pale and ulcerated. There was no rigidity of the neck. Examination of the thorax revealed apparently normal cardiac and pulmonary fields. There were no cardiac murmurs or adventitious sounds. The abdomen was apparently normal. On movement of the right leg there was great pain just below the knee and in the ankle, where redness and slight swelling were noted. The other extremities were not abnormal. Roentgen examination of the chest and of the right knee and ankle revealed no changes.

Laboratory Examination.—On February 4 the red blood cell count was 5,300,000, with hemoglobin content of 100 per cent (14.5 Gm., Sahli); the red cell count fell to 4,250,000 with a hemoglobin level of 88 per cent on the next day; by February 9 the red cell count had fallen to 2,970,000 and the hemoglobin content to 58 per cent. The white cell count, which was 7,000 on admission, rose to 17,200 on the next day, with the percentage of neutrophils rising from 75 to 95 during the same period. Urinalysis revealed occasional hyaline and granular casts. Smears taken from the gums revealed many Vincent's spirochetes and fusiform bacilli. Spinal fluid drawn on February 5 contained 50 cells per cubic millimeter, of which 47 were lymphocytes and 3 neutrophils. In a fixed smear of this fluid, gram-negative biscuit-shaped cocci arranged in pairs and tetrads were seen in a few neutrophils. The test for globulin gave a strongly positive reaction; the qualitative sugar reaction was negative. Examinations of spinal fluid were done daily thereafter; the cell count gradually rose to 2,800, the cell type changing to neutrophilic (96 per cent) as the count increased. Smears of the fluid showed more bacteria, and cultures on Veddar's starch agar gave good growths of the organisms, which were proved to be meningococci by the typical sugar fermentations. Cultures of blood drawn on February 5 and daily thereafter were all positive for meningococci.

Course of the Disease.—On February 5 Kernig's sign and Brudzinski's sign were elicited. The patient was given a total of 70,000 units of meningococcus antitoxin, 16 Gm. of sulfanilamide and 35 cc. of neoprontosil (disodium-4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′,6′-disulfonate). The temperature continued to rise, however, and was septic in type, and rigidity of the entire body developed. Multiple petechiae and hemorrhagic bullae soon appeared over the trunk and extremities. The temperature remained septic and reached 108 F. on two occasions. Death occurred on the seventh day in the hospital. The clinical diagnosis was meningococcic septicemia with meningitis and Vincent's infecton of the mouth.

Postmortem Observations.—Gross Examination: The body was fairly well developed and poorly nourished, weighing about 100 pounds (45.4 Kg.) and measuring 155 cm. in length. Body heat was present and rigor mortis absent. A few death marks were seen on the posterior aspect of the body. The skin of the entire trunk and of the extremities showed multiple petechiae and small hemorrhagic bullae surrounded by blue, green and purple edges. The fluid in the bullae was serosanguineous. When the peritoneal cavity was opened multiple petechiae were seen on all the serous surfaces. There was no evidence of peritonitis. Both the visceral and the parietal pleura showed multiple petechiae. No adhesions or free fluid was encountered. The pericardial cavity showed a few petechial hemorrhages on the parietal surface and contained about 3 cc. of clear straw-colored fluid. The heart weighed 163 Gm. The epicardial surface presented multiple petechiae. There were, especially on the left ventricle, a few areas ranging from white to yellow surrounded by hyperemic zones; these appeared to be early abscesses. Near the apex of the heart there were two large abscesses 4 and 5 mm., respectively, in diameter which were surrounded by smaller ones. They were raised above the surrounding surface, were fluctuant, and on section were seen to be

filled with yellowish white purulent exudate. The right ventricle was fairly soft. Section through the left ventricle revealed that the muscle was mottled with pale brown and red areas and that the fibrous tissue stood out prominently. The endocardium of both ventricles and auricles was smooth and glistening. On the proximal surface of the posterior leaflet of the mitral valve was an ulcerated area covered by thin and firm vegetations; this measured 7 by 10 mm. (fig. 1). In its center the ulcer had eroded through the valve. The other valves, the coronary arteries and the great vessels appeared grossly normal. The lung showed chronic passive congestion of the dependent portions, which were subcrepitant.

Fig. 1.—Ulceration of a leaflet of the mitral valve.

No areas of consolidation were seen grossly. The spleen weighed 330 Gm., was very soft and dark red and showed several areas of infarction which contained purulent material. The liver weighed 1,450 Gm. The surface was opaque, and the cut section had the characteristic appearance of cloudy swelling. There were multiple petechial hemorrhages in the gastric mucosa. No other changes were seen in the intestinal tract. The adrenal glands showed no gross changes. Each kidney weighed 118 Gm. and showed multiple areas of infarction, recent and old. Many of the recent infarcts were septic. The kidney tissue had a flea-bitten appearance. The sex organs showed no gross pathologic changes. The head was opened in the usual manner; reflection of the dura revealed intense hyperemia of the brain and leptomeninges. A small amount of fibrinous exudate was seen in the sulci of the cerebrum, especially over the temporal and parietal regions.

On section through the brain, intense hyperemia was observed in all parts. No gross abscesses were seen in the brain, and the cerebral venous sinuses were not thrombosed. The right knee and ankle joints were opened and examined. There was an increase of synovial fluid, which was turbid. The synovial membranes were hyperemic but smooth, and the surface appeared intact. No areas of destruction of tissue could be demonstrated in the joints. The anatomic diagnosis was

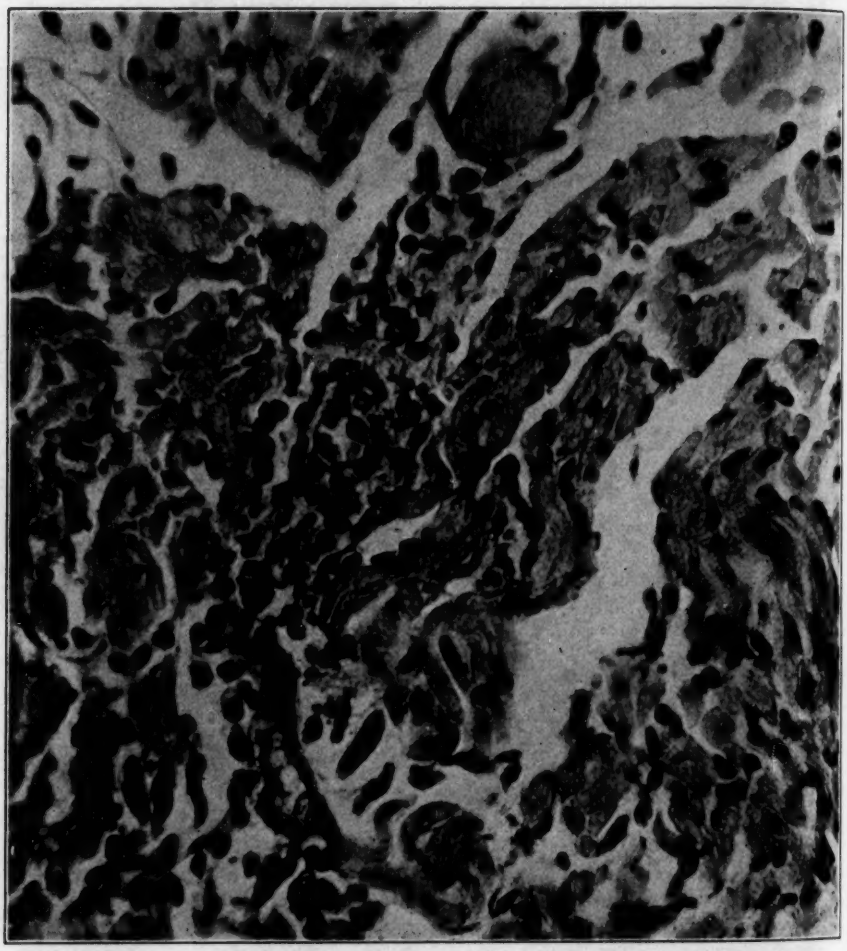

Fig. 2.—Acute interstitial myocarditis. Hematoxylin and eosin stain; × 400.

meningococcic septicemia with acute purulent meningitis, acute ulcerative endocarditis and suppurative myocarditis; septic infarcts of the spleen and kidneys; embolic glomerulonephritis, and serous polyarthritis.

Microscopic examination: Sections through the mitral valve showed an ulcerated area which was covered with a vegetation composed of inflammatory cells, fibrin and small masses of bacteria which in smears appeared to be meningococci. The base of the valve was densely infiltrated with lymphocytes, neutrophils and large mononuclear cells, and the vascularity was increased in this area. The myo-

cardium showed areas of early abscess formation characterized by bacteria surrounded by round cells and smaller numbers of neutrophils. There were also focal areas of infiltration by large mononuclears and lymphocytes in the interstitial tissue near small vessels (fig. 2). These areas had some resemblance to Aschoff bodies. Sections through the larger abscesses showed them to be filled with necrotic débris, bacteria and neutrophils, the wall being formed by neutrophils, fibrin and necrotic muscle fibers, which were greatly swollen and had lost their striations. The epicardium was thickened and contained a large amount of adipose tissue, which extended into the superficial layers of the myocardium and showed infiltration by a small number of inflammatory cells. Sections through the brain showed intense hyperemia of the brain substance and meninges. Between the arachnoid and the pia was an exudate composed of neutrophils, lymphocytes, large mononuclears and plasma cells, neutrophils being predominant. There was some destruction of the superficial layers of the cortex, and there were multiple small abscesses in the cortex and at the junction of the cortex and the white substance. The content of the abscesses was formed by neutrophils, lymphocytes and necrotic débris. Some areas showed marked collaring of the vessels by lymphocytes and neutrophils. Scattered throughout the entire kidney were abscesses due to bacterial emboli obstructing the glomerular tufts. These areas showed neutrophils, lymphocytes and bacterial masses which apparently were plugging the glomerular vessels. An occasional glomerulus was almost completely hyalinized. A few large abscesses contained only neutrophils and necrotic débris. The secretory tubules showed moderate parenchymatous degeneration. Sections of the liver showed a moderate degree of fatty metamorphosis and passive hyperemia. There were multiple focal areas of cellular infiltration composed of lymphocytes, large mononuclears and an occasional neutrophil. These areas were irregular in shape, size and location. No areas of central necrosis were seen. Sections of the spleen showed septic infarcts with numerous neutrophils and necrotic débris. The pulp was markedly engorged with red cells. The sections through the lungs showed interstitial pneumonia, evidenced by marked infiltration of the interstitial tissues with lymphocytes, large mononuclears and occasional neutrophils. The alveoli contained a minimum amount of exudate and a moderate amount of plasma. An occasional small infarct was seen which contained bacterial masses and necrotic débris. Sections through the intestinal tract showed an increased number of lymphocytes in the submucosa and a few small hemorrhagic areas in the mucosa. No ulcerations were present. Sections through the pancreas showed no pathologic changes.

Diagnosis.—The final diagnosis was meningococcic septicemia with meningoencephalitis, ulcerative endocarditis, suppurative myocarditis and pyemic metastasis to the spleen, lungs, kidneys, skin and liver; interstitial bronchopneumonia; pulmonary infarcts, and serous polyarthritis.

COMMENT

The articular pain, which was the first and most prominent clinical symptom in this case and which led to a diagnosis first of rheumatic fever and then of osteomyelitis, was stated by Swift [3] to be one of the common symptoms of meningococcic septicemia. Some have expressed the belief that it is a toxic reaction in the involved joint in the majority

3. Swift, H. F.: Meningococcus Endocarditis, in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1926, vol. 4, p. 332.

of cases, as destructive lesions are not noted at autopsy and only in rare instances do they develop in patients who recover. This same symptom was also described in the cases of Cecil and Soper, Finley and Rhea,[4] MacMahon and Burkhardt [5] and Gwyn.[2] The cardiac lesions usually involve the endocardium, more specifically, the mitral valve. In the reported cases the mitral valve was involved fourteen times, the aortic five times and the tricuspid only once; ulceration of the intraventricular septum occurred in 1 case. The majority of the valvular vegetations are large, bulky and firm. They have a hemorrhagic, edematous base, and there is dissolution of the muscle fibers immediately under them. In the case reported here there was a thin firm vegetative mass which barely covered the ulcerated area and had a central ulceration extending completely through the valve leaflet. Although it did not appear friable, it apparently gave off numerous embolic particles, as manifested by the large number of metastatic abscesses seen at autopsy. Involvement of the myocardium has been reported in association with endocardial lesions by Rhoads,[1] MacMahon and Burkhardt,[5] Stevenson,[6] Gwyn [2] and Bancker [7] and in the isolated form by Saphir,[8] Westenhoeffer, Ghon, Baehr and Klemperer.[9] The myocardial lesions consist of diffuse and focal accumulations of inflammatory cells, at times having the appearance of a rheumatic lesion, as pointed out by Saphir,[8] Bancker,[7] Gwyn [2] and Rhoads.[1] Near these focal areas the myocardial fibers are frequently fragmented and often have lost their striations. Occasional small areas of hemorrhage are seen throughout the sections. The diffuse infiltrations consist chiefly of lymphocytes and large mononuclears scattered through the interstitial tissue, which is often increased in amount. Many reports emphasize lesions of this type in other organs of the body. Large myocardial abscesses of the type seen in my case are rarely reported, presumably because the toxemia is overwhelming before they develop to this size. Interstitial pneumonia, as observed in my case, is not common; its cellular reaction, involving lymphocytes and large mononuclears with only a little exudate in the alveolar spaces, is comparable to the early changes produced by the meningococcus in other organs. The clubbing of fingers in the cases of more chronic meningococcic septicemia is possibly due to fibrosis

4. Cited by Rhoads.[1]

5. MacMahon, H. E., and Burkhardt, E. A., Jr.: Meningococcic Endocarditis, Am. J. Path. **5**:197 (May) 1929.

6. Stevenson, W. D. H.: A Case of Chronic Meningococcic Septicemia with Bacterial Endocarditis, Brit. M. J. **2**:1173 (Dec. 26) 1931.

7. Bancker, E. A., Jr.: Meningococcus Endocarditis, J. M. A. Georgia **19**: 480 (Nov.) 1930.

8. Saphir, O.: Meningococcus Myocarditis, Am. J. Path. **12**:677 (Sept.) 1936.

9. Cited by Saphir.[8]

of the lungs following the acute interstitial inflammatory changes, as seen in my case. Although meningococcic septicemia is almost always associated with meningitis, involvement of the brain is unusual. In my case the meningitic reaction was apparently subsiding, but destruction of the cortex and the medullary portion of the brain with formation of small abscesses and perivascular infiltrations of inflammatory cells was observed. The pathologic basis of the earliest symptom in this case—the severe pain in the ankle and knee joints—consists merely of exudation into the joint space without actual destruction of tissue.

CONCLUSIONS

Meningococcic endocarditis with myocarditis is an uncommon condition, usually rapidly fatal and occurring generally in the course of septicemia with meningitis. The described cardiac lesions are usually mitral in location, and the myocardial lesions are probably more common than is recognized at present. Metastatic lesions are not infrequent, although not often recognized clinically. The diagnosis of septicemia is generally made by blood culture during the clinical course, the endocarditis frequently being overlooked. Manifestations in the joints are common and often are misleading in an early diagnosis. The lesions in the other organs offer nothing unusual, merely giving proof of the great extension of the septic process. In the present case the short duration of the disease and the absence of clinical symptoms of cardiac involvement permit the conclusion that the involvement of the heart was merely another manifestation of the septicemia and should not be regarded as the primary visceral lesion.

INFECTION OF THE URINARY TRACT WITH BACILLUS DYSENTERIAE

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Infection of the urinary tract with Bacillus dysenteriae has been reported in 33 instances, exclusive of the case presented here. The findings are of sufficient interest to warrant tabulation.

It will be seen that of the 34 reported cases, in 16 the disease occurred in children, in 17 in adults and in 1 the age was not indicated. Of the adults, 4 were pregnant women. Twenty-one of the patients were females, 6 were males, and the sex of 7 was not stated. A history or signs of dysentery were obtained in 15 instances and positive fecal cultures in only 6. The following strains of the organism of dysentery were recovered from the urine: Flexner in 28 cases, Hiss in 3 cases, Sonne-Duval in 1 case, Shiga in 1 and Bacillus alcalescens in 1. From these facts the following inferences may be drawn: 1. Dysenteric infections of the urinary tract occur predominantly in females. 2. Children and adults are affected about equally. 3. Women are likely to be infected during pregnancy. 4. There is a marked paucity of concomitant fecal cultures. 5. A history or signs of dysentery are obtained in less than half the cases. 6. The predominating strain is B. dysenteriae Flexner. The case presented here is particularly relevant because in this instance too the patient was a female, without any known history or signs of previous dysentery and with negative sigmoidoscopic findings and fecal culture.

REPORT OF A CASE

L. M., a girl 22 months of age, was admitted to the pediatric service of Dr. Henry Heiman[1] on May 26, 1938, because of fever and refusal to take food since February. At the time of onset the temperature was 102 F. and was accompanied by vomiting. After several days the temperature rose, fluctuating between 100 and 106 F. This course persisted in somewhat modified form until the day of the patient's admission. The infant had always been breast fed and had developed normally, with no noteworthy indisposition previous to the onset of the present illness. There was never any diarrhea or evidence of a urinary disturbance.

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1. Dr. Henry Heiman and Dr. Martin J. Loeb made this case available for study.

Physical examination gave negative results. A catheterized specimen of urine contained albumin, acetone and many clumps of polymorphonuclear leukocytes. A diagnosis of pyelitis was made, and sulfanilamide therapy was instituted. The temperature fell on the day after admission, varying between 97 and 100.4 F.

Reported Incidence of Infection of the Urinary Tract *

Author	Reference	Age	Sex	History or Signs of Dysentery	Stool Culture	Urine Culture	Comment
Creighton and others	Bull. Johns Hopkins Hosp. **32**: 360, 1921	27 mo.	F	+	0	X	
Neter	J. Infect. Dis. **61**: 333, 1937	2½ yr.	F	0	H	H	Carrier
Neter	J. Infect. Dis. **61**: 333, 1937	7 yr.	F	0	0	X	
Neter	J. Infect. Dis. **61**: 333, 1937	32 yr.	F	0	H	H	Pregnant
Stewart	Am. J. Obst. & Gynec. **35**: 1887, 1938	20 yr.	F	0	0	X	Pregnant
Fränkel	Deutsche med. Wchnschr. **41**: 1182, 1915	Adults (4)	M	+	0	X	
Cheatham	Am. J. Obst. & Gynec. **28**: 448, 1934	25 yr.	F	0	X	X	Pregnant
Foerster	München. med. Wchnschr. **65**: 205, 1918	Adult	M	+	0	X	
Hilgers	Centralbl. f. Bakt. **83**: 414, 1919	Adult (1) Child (1)	F ?	Enteritis (1) ..	0 0	X X	
Calalb and Ionesco	Compt. rend Soc. de biol. **92**: 1460, 1925	Adult (1)	F	..	0	X	Pregnant
Tevell	Arch. f. Kinderh. **95**: 92, 1931	5 yr. (2) 10 yr. (1)	F	..	X (1)	X	
Tevell	Arch. f. Kinderh. **104**: 69, 1935	Children (4)	F	+	X (2)	X	
Sonne	Centralbl. f. Bakt. **75**: 408, 1915	Unknown (1)	?	..	..	X	Coincident Bacillus typhosus
Ghon and Roman	Wien. klin. Wchnschr. **28**: 579, 1915	Adult (1)	M	+	..	S	
Brunauer	Wien. klin. Wchnschr. **29**: 128, 1916	Adults (4)	M	+	X (2)	X (4)	Coincident Bacillus paratyphosus
Pacheco and Pecego	Brasil-med. **50**: 111, 1936	27 yr.	F	..	..	S-D	
Snyder and Hanner	J. Infect. Dis. **60**: 51, 1937	7 yr.	F	..	..	A	Brother's stool A
Dietrich	Am. J. Dis. Child. **56**: 270 (Aug.) 1938	3 yr.	F	0	..		
Dietrich	Am. J. Dis. Child. **56**: 270 (Aug.) 1938	5 yr.	F	0	..	X (3)	
Dietrich	Am. J. Dis. Child. **56**: 270 (Aug.) 1938	21 yr.	F	0	..	H (1)	
Dietrich	Am. J. Dis. Child. **56**: 270 (Aug.) 1938	12 yr.	F	0	..		
Felsen and Wolarsky	.....	22 mo.	F	0	0	X	

* F indicates female; M, male; X, B. dysenteriae Flexner; H, B. dysenteriae Hiss; S-D, B. dysenteriae Sonne-Duval; S, B. dysenteriae Shiga; A, B. alcalescens.

until operative intervention was deemed necessary. Pyuria persisted until July 9 in spite of medicinal therapy. On June 6 culture of a catheterized specimen of urine revealed the presence of a member of the dysentery group of organisms (B. dysenteriae Flexner). This finding was subsequently confirmed on five occasions. On three examinations Bacillus coli was isolated. In view of these findings, a sigmoidoscopic examination was performed on June 17, but it revealed no significant pathologic change. On June 22 an intravenous pyelogram showed no

excretion by the left kidney, which was considerably enlarged. The right kidney was normal. A retrograde pyelogram (fig. 1) disclosed the catheter coiled in the lower part of the left ureter, which was distended. After the injection of a radiopaque material, the left renal pelvis and calices and the upper part of the left ureter were seen to be markedly dilated. The condition was deemed amenable only to surgical therapy, and on July 20 nephrectomy was performed by Dr. M. J. Loeb.

The specimen measured 10 by 5 cm. and included 9 cm. of ureter (fig. 2). The surface of the kidney was somewhat nodular and felt cystic. The capsule

Fig. 1.—Retrograde pyelogram, showing the catheter coiled in the lower part of the dilated left ureter (outlined by the lower six arrows). The distended calices, pelvis and upper portion of ureter are indicated by the upper two arrows (Dr. William Snow).

stripped with ease, revealing one large and several smaller hemorrhagic areas on the surface. On section the kidney was observed to be hydronephrotic, most of the medulla being replaced by large cysts filled with thin cloudy fluid. The cortex measured 4 mm. in thickness. The ureter was greatly dilated, measuring 1.5 cm. in diameter, and the wall was thickened. The mucosa exhibited numerous pinpoint hemorrhages. Received separately was a portion of ureter 6 cm. in length, with changes similar to those just described. Culture of fluid in the renal pelvis

revealed B. dysenteriae. The histologic alterations (fig. 3) consisted chiefly of atrophy of the renal parenchyma with marked thinning of the tubular epithelium and diffuse as well as focal infiltration with polymorphonuclear and mononuclear cells. Many of the tubules were cystic and filled with these cells. The glomeruli were rather well preserved, except for some atrophic, shrunken tufts just beneath the capsule of the kidney. The wall of the ureter exhibited marked interfascicular fibrosis, with rather superficial and some deep cellular infiltration.

The patient made an uneventful recovery and was discharged well on August 9, nineteen days after operation and seventy-five days after admission. Culture of

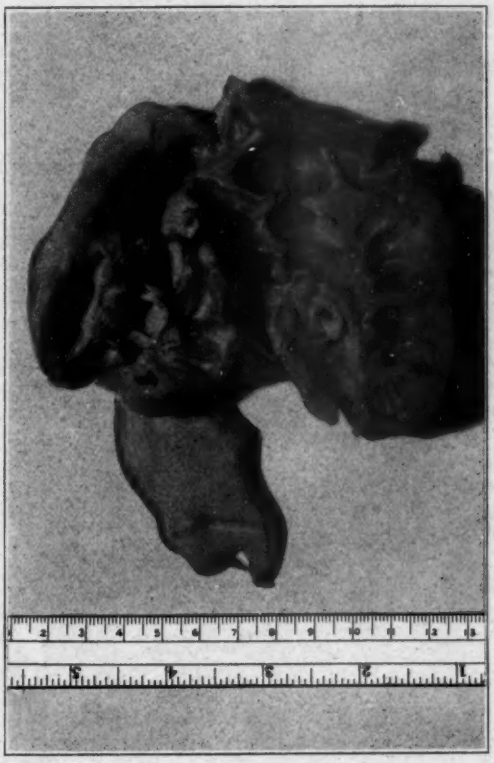

Fig. 2.—The hydronephrotic cystic kidney, with a portion of the dilated thickened ureter.

urine obtained seven days postoperatively yielded B. dysenteriae, after which 2 other cultures were negative for the same organism. A total of 4 fecal cultures and 1 culture [2] of material obtained by sigmoidoscopic aspiration of the cypt were likewise negative.

Follow-up studies were carried out thirty-five and fifty days after the infant's discharge from the hospital. The culture of the urine remained negative. The wound was completely healed, and the child was gaining weight.

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2. Felsen, J.: Crypt Aspiration: Spray Culture Method for the Isolation of B. Dysenteriae, J. Lab. & Clin. Med. **23**:630 (March) 1938.

Repeated but unsuccessful efforts were made to study the mother, father, sister, grandmother and uncle, all of whom lived with the infant, in an attempt to ascertain the epidemiologic aspects of the case.

The studies on agglutination are of particular interest, as they established the specific strain of B. dysenteriae involved. The infant's blood agglutinated B.

Fig. 3.—Photomicrograph, showing atrophic renal parenchyma and glomeruli with focal and diffuse infiltration by polymorphonuclear and mononuclear cells. Cystic changes are clearly evident.

dysenteriae Mount Desert to a titer of 1 : 160. This is significant, since our previous experience has shown an extremely low incidence of diagnostic titers against B. dysenteriae among children of the sheltered age group. The organism which was isolated from the urine belonged to the mannitol-fermenting group, showed a rather constant acidification of rhamnose and agglutinated in monovalent Sonne-Duval serum to a titer of 1 : 640. It gave a higher titer (1 : 1,280), however, to

monovalent Mount Desert serum. The differentiation was rendered rather difficult, as such high titers against B. dysenteriae Sonne-Duval are uncommon with a serum of Flexner type. Although fermentation of rhamnose was constant, the organism did not give the characteristic late fermentation of lactose (after one week). We felt certain that we were dealing with a single strain. The titer of the infant's blood against the autogenous Mount Desert strain as well as the higher titer of the monovalent serum against the same organism impelled us to classify that recovered from the urine as B. dysenteriae Flexner (Mount Desert). The probable explanation of this interesting cross agglutination phenomenon lies in the antigenic heterogeneity of the mannitol-fermenting group of dysentery organisms. Since B. dysenteriae Flexner Y contains at least six antigenic components (Flexner V, W, X, Y and Z and Sonne-Duval), it is theoretically possible for anti-Flexner serum to agglutinate the Sonne-Duval organism. The reverse, however, does not generally occur, as the latter organism contains only a single antigen.

In general, renal infection appears to take place by the ascending route, particularly in females. In the rare cases of dysentery bacillemia hematogenous involvement of the kidney probably occurs. This was apparently the mechanism in the case reported by Ghon and Roman, in which the patient was a soldier with acute bacillary dysentery and positive cultures of both urine and blood were obtained. It is of interest to note that the Shiga strain was recovered from the urine and the Flexner Y from the blood, which indicates a rather unusual type of double infection.

The absence of history or clinical signs of bacillary dysentery, observed in more than half of the reported cases, does not rule out the disease. It may be due to failure to recognize the atypical forms of the disease and the characteristic progressive three stage intestinal change.[3] The atypical varieties include the mild Sonne-Duval type [4] and asymptomatic,[5] afebrile,[5] constipated,[5] meningitic,[5] pneumonic,[6] appendicular [7] and agranulocytoid [8] forms. Carriers of B. dysenteriae are "sick carriers" in the sense that they have had the acute form of the disease and often are suffering from the chronic form. The asymptomatic, afebrile or constipated type always exhibits in the rectosigmoid part

3. Felsen, J.: Acute and Chronic Bacillary Dysentery, Am. J. Path. **12**:395 (May) 1936.

4. Felsen, J., and Osofsky, A. G.: Sonne Dysentery, J. A. M. A. **103**:966 (Sept. 29) 1934.

5. Felsen, J.; Rundlett, E. V.; Sullivan, J., and Gorenberg, H.: Atypical Flexner Dysentery: A Preliminary Report of the Jersey City Epidemic, J. A. M. A. **103**:1055 (Oct. 6) 1934.

6. Felsen, J.: The Pneumonic Type of Bacillary Dysentery, New York State J. Med. **37**:253 (Feb. 1) 1937.

7. Felsen, J.: Appendicular Form of Bacillary Dysentery, with Notes on Mesenteric Adenitis and Inflammation of the Distal Portion of the Ileum, Am. J. Dis. Child. **50**:661 (Sept.) 1935.

8. Felsen, J.: Bacillary Dysentery: Acute Fulminating Type with Marked Toxic Neutropenia, New York State J. Med. **35**:1037 (Oct. 15) 1935.

of the colon at least one or two of the typical three stages: (1) punctate follicular hyperplasia, (2) punctate follicular necrosis and (3) discrete and confluent ulceration. In addition, there are a rising agglutination titer, a positive culture at the onset and a typically polymorphonuclear mucosal exudate. The absence of positive fecal cultures is readily explained on the basis of nonrecognition of the disease and the frequently transitory existence of the organism even in typical cases.

Infection of the urinary tract with B. dysenteriae depends to a large extent on the p_H of the urine. Although minor adaptations may occur in some instances, the Flexner organism does not survive a p_H of 4.5 to 5.5. It multiplies rapidly as the urine approaches alkalinity and disappears with sustained acidities greater than p_H 5.5. This explains the effectiveness of mandelic acid—ammonium chloride therapy and the spontaneous disappearance of the organism, which sometimes occurs. It is of interest to note that in our case the urine was alkaline during the period of positive cultures and acid (p_H 6.8) after nephrectomy, when the cultures became negative. Infection of the urinary tract is more common with acute and chronic bacillary dysentery than is generally supposed, but in our experience the enterococcus and B. coli have been the usual invaders.

The ideal treatment of renal infections of this type clearly lies in the prevention of bacillary dysentery.[9] Every patient with the acute disease whose urine contains polymorphonuclear leukocytes should receive the benefit of repeated cultures. If they are positive, the infection should yield promptly to mandelic acid—ammonium chloride therapy supplemented by limitation of fluids to 1,000 cc. daily. Frequent tests must be made in order that one may be certain that the p_H remains at 5.3 or less until repeated cultures prove sterile. Early and prompt eradication will prevent such late complications as ureteral stricture, hydronephrosis and pyelonephritis.

SUMMARY

Thirty-three reported cases of infection of the urinary tract with B. dysenteriae, supplemented by 1 of our own, are reviewed.

The general features are the predominance of female patients, the frequent absence of history or signs of dysentery, the marked prevalence of B. dysenteriae Flexner and a paucity of concomitant fecal cultures.

Our patient, a girl of 22 months, was cured by the removal of the infected kidney and ureter, follow-up studies indicating the disappearance of the dysentery organism from the urine.

The general new clinical and laboratory features of acute bacillary dysentery are described, and their applicability to diagnosis and to preventive and curative therapy is suggested.

9. Felsen, J.: Prevention and Control of Outbreaks of Bacillary Dysentery, Hospitals **11**:27 (March) 1937.

Progress in Pediatrics

ACUTE SUPPURATIVE THYROIDITIS DURING CHILDHOOD

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Acute suppurative thyroiditis is a relatively rare disease, since suppuration does not always follow acute thyroiditis. Acute *thyroiditis* is an inflammatory process, usually due to infection, in a previously normal thyroid gland. In contradistinction is *strumitis,* an inflammatory process, usually due to infection, in a nodular goiter. In cases in which suppuration does occur, the degree of subsequent metabolic disturbance depends on the extent of cellular destruction as well as the resultant fibrosis.[1] Awareness of these deficiency effects is important in the follow-up management of such patients, since subsequent hypofunction of the thyroid is likely to occur.

Ensuing damage to the thyroid gland has particular significance in young children, in whom adequate thyroid function is essential for normal growth and mental development.[2] Thyroid hypofunction early reveals itself in terms of decreased pulse rate, decreased metabolic rate in the resting state and a decrease in the blood iodine.[3] In children, later there insidiously appear mental retardation, lethargy, poor skeletal growth as revealed by roentgen studies [2b] and a subnormal increase in weight. By well spaced determinations of the metabolic rate during the resting state, of the blood iodine and of the pulse rate during a

From the Department of Research Surgery, the Ohio State University.

Read before the Detroit Academy of Surgery at the University Hospital on April 3, 1939.

This work was aided by a grant from the Comly Fund for Medical and Surgical Research of the Ohio State University.

1. (*a*) McCarrison, R.: The Thyroid Gland, New York, William Wood & Company, 1917. (*b*) de Quervain, F.: Goiter: A Contribution to the Study of the Pathology and Treatment of the Diseases of the Thyroid Gland, translated by J. Snowman, ibid., 1924.

2. Shelton, E. K.: (*a*) Osseous Development as an Index of Metabolic Speed, Endocrinology **17**:667 (April) 1933; (*b*) Osseous Development as an Index of Metabolism, Radiology **20**:241 (April) 1933.

3. Curtis, G. M.; Barron, L. E., and Phillips, F. J.: Blood Iodine Studies: V. The Blood Iodine After Total Thyroidectomy in Man, J. Lab. & Clin. Med. **20**:813 (May) 1935.

follow-up period of several months, the extent of the diminished thyroid function, if any, can be ascertained, and suitable therapy can be instituted to insure normal development. The adequacy of the therapy can be determined by these same studies along with determination of height and weight curves over a period of years. A case is presented to emphasize these points.

REPORT OF A CASE

History.—A 10 year old boy had had measles, acute epidemic parotitis and varicella during his earlier childhood. In 1925 he had an appendectomy, a herniorrhapy and an adenoidectomy. In 1933 he had a tonsillectomy. On July 15, 1936, he was seen by his family physician because of pharyngitis of twenty-four hours' duration. At that time the posterior pharyngeal surface was reddened, and there was inflammation of the tonsillar remnants. These were painted with an antiseptic solution, and benzoin inhalations were instituted. During the ensuing week the patient became more acutely ill. He began to have difficulty in deglutition; his voice became hoarse, and he held his chin down and his head rigid. A daily rise in temperature to 100 F. was noted. The family physician found that the redness of the pharynx had become more diffuse. There was, in addition, a hard tender swollen area about 2 cm. in diameter involving the thyroid isthmus. Cold compresses were then applied to the neck for several days.

On July 29 the boy was seen in consultation with Dr. John W. Larcomb at the University Hospital. At that time he presented a septic appearance, with a temperature of 103 F., a rapid pulse, dilated cervical veins, enlarged deep cervical lymph nodes and a diffusely enlarged, firm, adherent, very tender indurated swelling involving the entire thyroid gland. The heart and lungs were clear. A diagnosis of acute thyroiditis was made. It was advised that the cold applications be continued but that the boy be hospitalized should the process go on to suppuration. Three days later fluctuation became evident over the isthmus, and the child was admitted to the Research Surgical Service of the University Hospital.

Physical Examination.—On the patient's admission the temperature was 103 F., the pulse rate 118, the respiratory rate 24, the blood pressure 102 systolic and 60 diastolic and the weight 30.5 Kg. The gums, lips, teeth and tongue were clear. The tonsillitis and pharyngitis had subsided. Fluctuation was noted over the isthmus of the otherwise indurated thyroid gland, while the overlying skin had become reddened. The other signs were as found at the consultation three days previously.

Laboratory Findings.—The hemoglobin content (Sahli) was 100 per cent; red blood cells numbered 5,120,000 and white blood cells 7,000, with a differential count of 50 per cent polymorphonuclears; 33 per cent lymphocytes; 13 per cent monocytes; 1 per cent eosinophils and 3 per cent basophils. The urine was normal. The Wassermann and Kahn reactions of the blood were negative.

Course.—Since the diagnosis of suppurative thyroiditis was evident, further delay was considered hazardous, and the patient was prepared for operation on the evening of the day of admission (August 1). With preliminary administration of morphine sulfate followed by local anesthesia, a median transverse incision 2 cm. in length was made at the lower margin of the fluctuant area. The sternohyoid and sternothyroid muscles were exposed and separated, and an aspirating needle was inserted through the outer thyroid capsule. About 30 cc. of thin yellow foul-smelling purulent material was obtained. The abscess was then

widely opened. On careful exploration both lobes of the thyroid, as well as the isthmus, were found to be involved. A split Penrose drain was then inserted into the abscess cavity, and a dry dressing was applied. The patient returned to his room without evidence of respiratory difficulty.

A direct smear of the pus obtained at operation revealed gram-positive cocci as well as gram-negative and fusiform bacilli.

The abscess cavity was subsequently irrigated daily with dilute solution of sodium hypochlorite. The patient's condition subsequently improved. The drainage diminished and then gradually ceased. The boy was discharged on August 4, with a temperature of 98 degrees F., a pulse rate of 72 and a respiratory rate of 18. In view of the possible eventual development of thyroid hypofunction, he was instructed to return to the outpatient clinic for follow-up study and treatment as required.

On August 15, two weeks after operation, the temperature was 98.2 F., the pulse rate 66, the respiratory rate 12, the blood pressure 82 systolic and 72 diastolic and the basal metabolic rate —7. The incision had healed well, with no residual induration, and the patient had no complaints. However, one week later he complained of nausea, general malaise and lethargy. Examination at this time

*Average Heights and Weights of Normal Boys from Ten to Thirteen Years of Age**

Age, Yr.	Height, Cm.	Weight, Kg.
10	132.7	30.3
11	137.2	32.9
12	141.6	36.2
13	145.0	37.5

* From tables of the Bureau of Education, Department of the Interior, Washington, D. C. (Davison, W. C.: The Compleat Pediatrician, Durham, N. C., Duke University Press, 1934).

revealed that the temperature was 98 F., the pulse rate 65, the respiratory rate 11, the blood pressure 90 systolic and 40 diastolic and the basal metabolic rate, —13, a value which indicated that the rate was decreasing. During the next two months the basal metabolic rate gradually fell to —16 and the blood iodine from a normal value of 3.8 to 2.4 micrograms per hundred cubic centimeters. The boy then presented clinical evidence of beginning thyroid hypofunction. Although he did not feel as well as usual, he showed no myxedema, obvious mental retardation or physical sluggishness. In order that further evolution of the hypothyroidism might be prevented, the patient was put on a regimen of 1 grain (0.06 Gm.) of desiccated thyroid daily and 10 mg. of iodine weekly, the latter in the form of oridine tablets.

Follow-up studies of the patient's metabolism and growth were made during the next two years and eight months. Except for one period during the summer of 1938, during which the patient neglected his medication, a relatively normal metabolism has been maintained, as can be seen in figure 1. Mental development has been normal throughout, and height and weight have been above the average.

That the patient's height and weight have been above average can be seen by comparing the values for his height and weight during the period of study (fig. 1) with the average values for boys of corresponding age as given in the tables of the Bureau of Education, Department of the Interior (table). When the incipient hypothyroidism was discovered in this patient, his weight and height were slightly greater than the average values. After the first year of thyroid

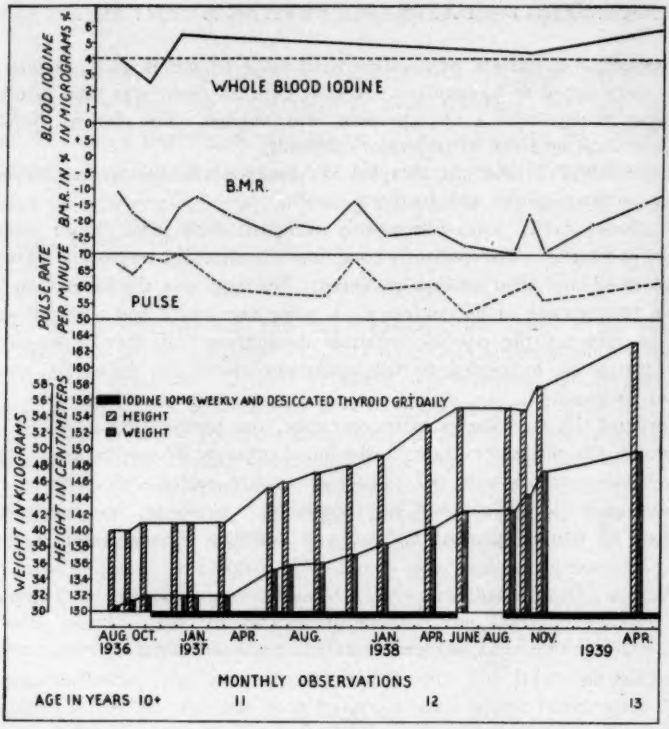

Fig. 1.—The effects of iodine and desiccated thyroid therapy for hypothyroidism subsequent to acute suppurative thyroiditis in a 10 year old boy. Data are given on growth and metabolism after operation on Aug. 1, 1936. (A microgram is equivalent to 0.001 mg.)

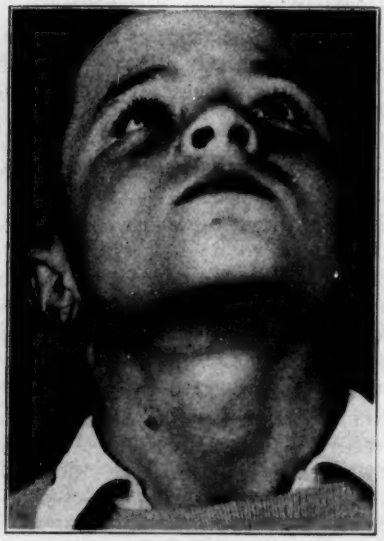

Fig. 2.—The patient after two years of therapy, with normal appearance and absence of a deforming scar.

and iodine therapy he was 9 cm. taller and weighed 3 Kg. more than was expected, while at his last visit, at the age of 13, he was 17 cm. taller and 11.5 Kg. heavier than the average boy of that age.

An April 21, 1939, two years and eight months after the drainage of the suppurative process, the patient was hospitalized for final investigation. The basal metabolic rate was —11, the height 162 cm., the weight 49 Kg. and the pulse rate 60. The blood cell volume was 44 per cent. The iodine content of whole blood was 5.5 micrograms per hundred cubic centimeters, 4.5 micrograms per hundred cubic centimeters, or 82 per cent of the total, being present as serum iodine. The total twenty-four hour output of urinary iodine on April 22 was 424 micrograms and on April 23 was 381 micrograms. Roentgenograms of the hands showed normal bone markings, calcification and epiphyseal lines. These corresponded to those of a boy of 15 years. The blood calcium value was 11 mg. per hundred cubic centimeters, the blood phosphorus 5.4 mg. per hundred cubic centimeters and the blood phosphatase 19.5 King units.

COMMENT

As early as the eighteenth century a distinction was made between infection in previously goitrous thyroids and that in normal glands. The former was referred to as strumitis and the latter as thyroiditis.[4] Even in the face of this simple classification, however, confusion still exists between the two, which makes evaluation of certain reports difficult. However, there appears to be general agreement that primary acute thyroiditis is rarely seen.[5] The disease follows, or is associated with, infection elsewhere in the body. As early as 1878 Theodore Kocher pointed out that acute thyroiditis is due to the metastasis of an infectious agent from elsewhere in the organism, although he had no bacteriologic proof for this.[6] In 1892 one of his assistants, Tavel, proved his postulate by extensive bacteriologic studies.[7]

One could give a long list of infectious diseases following which inflammation of the thyroid has been known to occur. It is now known that nearly all sources of infection in the body can give rise to secondary thyroid inflammation.[1b] Infection in the thyroid gland is most frequent after pneumonia of any type. When the etiologic agent is a virus, as in measles or in chickenpox, the infection does not ordinarily progress to

4. Crotti, A.: Thyroid and Thymus, ed. 2, Philadelphia, Lea & Febiger, 1922, pp. 98-112.

5. (*a*) Ochsner, A. J., and Thompson, R. L.: The Surgery and Pathology of the Thyroid and Parathyroid Glands, St. Louis, C. V. Mosby Company, 1910. (*b*) Quervain.[1b] (*c*) Weinstein, M. L.: Acute Suppurative Thyroiditis with Report of One Case, Illinois M. J. **63**:275 (March) 1933.

6. Kocher, T.: Zur Pathologie and Therapie des Kropfes, Deutsche Ztschr. f. Chir. **10**:191, 1878.

7. Tavel, E.: Ueber die Aetiologie der Strumitis: Ein Beitrag zur Lehre von den haematogenen Infectionen, Basel, C. Sallmann, 1892.

suppuration. When typhoid fever was prevalent, typhoid thyroiditis was occasionally encountered.[8] Cases have been reported in which the condition followed erysipelas,[9] pneumonia,[10] tonsillitis, pharyngitis, influenza and puerperal septicemia,[11] diphtheria, acute rheumatic fever and malaria.[12]

The relative rarity of thyroiditis may possibly be explained by the anatomic and physiologic protection of the thyroid gland. The thyroid is well encapsulated by the fascial compartments of the neck, and, except in those rare instances in which persistence of the embryologic thyroglossal duct is noted,[13] there is no direct communication with the pharynx. Moreover, the thyroid has an unusual lymphatic system, which enables the gland to be drained to a degree unequaled in any other parenchymatous organ, viz., the specialized anastomotic arrangement of the lymph capillaries within the thyroid lobule.[14] Also, an extremely rich blood supply and the increased concentration of iodine as well as the production of the thyroid hormone tend to prevent infection in this organ. Nevertheless, the unusual bactericidal function and mechanical protection supposedly present may be disturbed by physiologic strain, as at puberty or during pregnancy, or by virulent infection elsewhere in the body. There is also some evidence that the thyroid's defense mechanism can be broken down by trauma.[15]

Infection may occur by way of the blood stream,[16] by way of a persistent thyroglossal duct,[13] by contiguity,[16a] by direct infection through penetrating wounds [16a] or by the metastatic spread from tonsillitis, pharyngitis and alveolar abscess.[15a]

Acute thyroiditis usually subsides in about one week, becomes chronic or goes on to suppuration. When suppuration does occur, it is usually

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8. Armstrong, E. G., in Keen, W. W.: Surgery: Its Principles and Practice, Philadelphia, W. B. Saunders Company, 1917, vol. 6, p. 997.

9. Weeks, L. M.: A Case of Erysipelas Terminating in Acute Thyroiditis, Brit. M. J. **2**:476 (Sept. 25) 1920.

10. Coope, R., and Findlay, L.: Acute Suppurative Thyroiditis, Lancet **1**: 1172 (May 23) 1936.

11. Burhans, E. C.: Acute Thyroiditis, Surg., Gynec. & Obst. **47**:478 (Oct.) 1928.

12. Robertson, W. S.: Acute Inflammation of the Thyroid Gland, Lancet **1**:930, 1911.

13. Meeker, L. H.: Infection Through a Persistent Thyroglossal Duct, Am. J. Path. **1**:57 (Jan.) 1925.

14. Williamson, G. S.: The Applied Anatomy and Physiology of the Thyroid Apparatus, Brit. J. Surg. **13**:466 (Jan.) 1926.

15. (*a*) Thorburn, I. B.: Acute Thyroiditis Following Teeth Extraction, Brit. M. J. **1**:428 (March 10) 1934. (*b*) Kocher.[6]

16. (*a*) Rogers, L.: Suppurative Thyroiditis, Lancet **1**:868 (April 23) 1927. (*b*) Coope and Findlay.[10]

confined to one lobe, but it may spread to the other. Cases have been reported in which only the pyramidal lobe was involved.[17]

The signs and symptoms of acute thyroiditis have been described as fever, pain over the thyroid gland, swelling of one or more lobes, tenderness, chills with fever, cough, hoarseness due to involvement of the inferior laryngeal nerve, dyspnea and dysphagia due to pressure, hyperthyroidism, dilated cervical veins, cervical lymphadenopathy and, if the process goes to suppuration, fluctuation and reddening of the overlying skin. Burhans, in a study of 67 cases of thyroid infection collected from the literature, found some or even all of these signs present.[11] Lahey, in 1917, called attention to two important signs, always present in suppurative thyroiditis, which he considered of diagnostic significance.[18] The patient is able to elevate the chin only with great pain and difficulty or not at all, and the chin is depressed on the sternum in order that deglutition may be accomplished. This appears to be due to the pressure of the sternohyoid and sternothyroid muscles on the abscess. Since publication of Lahey's article many of the case reports have included these signs.

The incidence of acute thyroiditis with subsequent suppuration is rare. Hagenbuch[19] reported 30 cases of thyroid suppuration, in only 5 of which there was no previous goiter. Robertson[12] collected 40 cases from the literature; in only 13 of these were the glands previously normal. Burhans[11] in a collection of 63 cases of thyroid suppuration in the decade preceding 1928 found only 39 in which the glands were previously normal. Clute and Smith[20] reported that in a series of 3,000 thyroid operations at the Lahey Clinic only 3 glands were treated for suppuration and only 1 was found to have no previous adenoma. Henderson[21] reported that in 4 of 545 thyroid glands operated on at the New York Post-Graduate Medical School and Hospital suppuration followed acute thyroiditis. Crile and others[22] reported that in a series of 10,000 operations on the thyroid gland suppuration was noted in 74 cases. In 11 cases there was previous adenoma. Rogers[16a] reported 2 cases of thyroid suppuration, in 1 instance in a previously normal

17. Hein, L.: Thyroid Abscess Involving Pyramidal Lobes, Laryngoscope **26**: 1020, 1912.

18. Lahey, F. H.: Thyroid Abscess with Mention of Two New Signs in This Condition, Boston M. & S. J. **176**:94 (Jan. 18) 1917.

19. Hagenbuch, M.: Strumitis, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **33**:181, 1921.

20. Clute, H. M., and Smith, L. W.: Suppurative Thyroiditis, Surg., Gynec. & Obst. **44**:23 (Jan.) 1927.

21. Henderson, J.: Abscess of Thyroid, Am. J. Surg. **29**:36 (July) 1935.

22. Crile, G. W., and others: Diagnosis and Treatment of Diseases of the Thyroid Gland, edited by A. F. Rowland, Philadelphia, W. B. Saunders Company, 1932.

thyroid gland. In a case reported by Porter [23] a thyroid abscess occurred in a previously nodular goiter.

The disease is most frequent between the ages of 20 and 40 years. In children the incidence is exceedingly low; however, several cases have been reported of children as young as 18 months. Henderson [21] reported occurrence in a child aged 2 years and in a girl of 15. Robertson [12] reported 2 cases of children less than 2 years of age, and Burhans [11] in his collection of 63 cases reported only 2 occurrences in the group less than 10 years of age and only 7 in the group between the ages of 10 and 20 years. Weinstein [5c] reported a case in a girl 3 years of age.

The suppurative process may involve the interstitial tissue, the parenchyma or, as usual, both.[24] Therefore one would expect subsequent metabolic disturbances in certain of these patients, which, particularly in children, would be accompanied by interference with growth and by mental retardation. But slight mention is made of this in the literature, and no detailed reports were found dealing specifically with such sequelae. Weeks [9] reported myxedema in a 46 year old white woman subsequent to incision and drainage of an abscess followed by the development of a sinus. This cleared after the sinus closed. No metabolic studies or treatment were included. There are warnings of subsequent hyperthyroidism [25] and mention that hypofunction of the thyroid may follow suppurative thyroiditis [26] while Robertson [12] went so far as to suggest that in certain cases cretinism and myxedema date from infections of the thyroid gland occurring during childhood.

Incision and drainage is the accepted treatment for the suppurative state.[5c] Kocher [6] even suggested extirpation of the diseased site. This may be necessary in case of strumitis, particularly if the abscess involves a calcified nodule, but it is not indicated for acute suppurative thyroiditis, since there is already destruction of the parenchyma, which may be of sufficient extent to cause subsequent lowering of the metabolism, as occurred in our patient.

The successful drainage and healing of the suppurative process are only the beginning. The follow-up study and treatment may be just as important as the immediate operative procedure, especially if the patient is a growing child. The operative intervention prevents too great destruction of the thyroid gland, but by careful study of the patient

23. Porter, M. F.: Old Nodular Goiter Surrounding Trachea, Posterior to the Carotid with the Isthmus Posterior to the Esophagus: Report of a Case with Sudden Death from Acute Abscess, Arch. Surg. **19**:466 (Sept.) 1929.

24. Burhans.[11] Clute and Smith.[20]

25. (*a*) Searls, H. H., and Bartlett, E. I.: Thyroiditis, California & West. Med. **24**:639 (May) 1926. (*b*) Crotti.[4]

26. Quervain.[1b] Ochsner and Thompson.[5a] Rogers.[16a] Henderson.[21] Crile and others.[22] Weinstein.[5c] Searls and Bartlett.[25a]

for several months after operation the extent of the damage in terms of thyroid hypofunction can be ascertained, and with adequate therapy the effects of the lowered metabolism can be counteracted and the patient's normal development can be safeguarded.

The theory that an adequate iodine intake is essential to the normal function of the thyroid gland has become widely accepted. As would be expected from studies of iodine metabolism in thyroid disease, along with the decreasing metabolic rate of our patient there was a diminution of the blood iodine, from 3.8 micrograms per hundred cubic centimeters three weeks after the suppurative process was drained to 2.4 micrograms two months later. By the newer method of Matthews [27] now used in our clinic, the normal human blood iodine ranges around 4 micrograms per hundred cubic centimeters. Curtis, Barron and Phillips [3] found that after total thyroidectomy for cardiovascular disease the blood iodine decreased to about one-third its normal level. These results were obtained by our older method,[28] which gave higher values for the blood iodine than those obtained by the new method, which was used in this case. It is not unreasonable, then, to deduce from the findings presented that the destruction of the boy's thyroid parenchyma by the suppurative process acted as a partial thyroidectomy. With the administration of small amounts (10 mg.) of iodine weekly, the iodine in the blood was maintained at a level slightly above normal (fig. 1). This appears to act as a valuable adjunct to thyroid therapy.

Previous studies have shown that the normal twenty-four hour urinary output of iodine in central Ohio ranges from 36 to 78 micrograms and averages 51 micrograms.[29] This physiologic variation may occur as a result of changes in the quantity and quality of the iodine intake, the activity of the thyroid gland, the breakdown of the thyroid hormone in the extrathyroid tissues or the excretion of iodine through other channels, principally in the feces and sweat.[30] Increased urinary excretion of iodine may be observed in hyperthyroidism,[31] in lymphatic

27. Matthews, N. L.; Curtis, G. M., and Brode, W. R.: The Determination of Iodine in Biological Materials, Indust. & Engin. Chem. **10**:612 (Oct. 15) 1938.

28. (*a*) Phillips, F. J., and Curtis, G. M.: The Clinical Determination of Iodine in Blood, Urine and Feces, Am. J. Clin. Path. **4**:346 (July) 1934. (*b*) Curtis, G. M.; Davis, C. B., and Phillips, F. J.: Significance of the Iodine Content of Human Blood, J. A. M. A. **101**:901 (Sept. 16) 1933.

29. (*a*) Curtis, G. M.; Puppel, I. D.; Cole, V. V., and Matthews, N. L.: The Normal Urinary Iodine of Man, J. Lab. & Clin. Med. **22**:1014 (July) 1937. (*b*) Curtis, G. M., and Puppel, I. D.: The Urinary Iodine in Thyroid Disease, West. J. Surg. **45**:417 (Aug.) 1937.

30. Puppel, I. D., and Curtis, G. M.: Calcium and Iodine Metabolism in Thyroid Disease, Arch. Int. Med. **58**:957 (Dec.) 1936.

31. Curtis, G. M., and Puppel, I. D.: Increased Urinary Excretion of Iodine in Hyperthyroidism, Arch. Int. Med. **60**:498 (Sept.) 1937.

and myelogenous leukemia,[32] in essential hypertension, hypertensive heart disease or, in certain cases, congestive heart failure,[32] after thyroidectomy [32] and after the administration of thyroid or iodine medication in any form.[29a] The medication explains the increased urinary output of iodine in our case, since the patient was taking both iodine and desiccated thyroid. That a normal iodine balance was maintained, however, is evidenced by the high level of iodine in whole blood as well as by the level found in serum at the last examination. This tendency of a normal person to store iodine after being in a negative iodine balance, which has been demonstrated in a previous communication,[33] supports the rationale of prescribing small amounts of iodine along with thyroid therapy. The resultant normal growth of our patient, as evidenced by the increase in his weight and height to levels above average for his age during the period of follow-up study (fig. 1, table), the normal skeletal development as seen in the roentgenograms of the extremities and the normal bone activity as evidenced by the phosphatase in his blood [34] are evidence of the adequacy of the therapy used in this case.

SUMMARY AND CONCLUSIONS

A case of acute suppurative thyroiditis in a child is presented which emphasizes the following points:

1. Hypofunction of the thyroid gland may follow acute suppurative thyroiditis.

2. The blood iodine falls below normal in patients presenting hypofunction of the thyroid gland.

3. Acute suppurative thyroiditis is thus of subsequent significance in growing children.

4. The administration of desiccated thyroid will maintain adequate thyroid function and elevate the blood iodine, permitting subsequent normal growth to occur.

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32. Curtis, G. M., and Barron, L. E.: The Urinary Loss of Iodine Following Total Thyroidectomy, Surgery **1**:92 (Jan.) 1937.

33. Curtis, G. M., and Puppel, I. D.: The Iodine Metabolism in Exophthalmic Goiter, Ann. Surg. **108**:579 (Oct.) 1938.

34. Knierim, H., and Curtis, G. M.: Unpublished data.

Abstracts from Current Literature

Biochemistry, Bacteriology and Pathology

PRECISE EVALUATION OF THERAPEUTIC ANTIPNEUMOCOCCAL SERA. K. GOODNER, C. M. MACLEOD, P. B. BEESON and C. L. HOAGLAND, J. Bact. **36**:276 (Sept.) 1938.

The generally accepted evaluation of antipneumococcus serums is based on the mouse protection system. This evaluation can be carried out rather accurately for any one serum of any one type, provided an arbitrary value is assigned to a reference serum and provided enough mice are used for each test. The authors feel that there are two major objections to this system: (1) There is no reference of potency from serum of one type to another and (2) the test is expensive if it is carried out in such a way as to give precise results. The solution of the problem, they state, appears to be the immunochemical precipitation method of Heidelberger, Sia and Kendall. Each milligram of antibody protein in antipneumococcus rabbit serum (type 1) is equivalent to 185 units. Horse serums fall into two groups. The serums of group A have the value of 85 units per milligram of antibody protein, while those of group B have the value of 135 units per milligram. These groups can be distinguished readily by the use of nonspecific antigens, such as sulfanilic acid combined with a protein, or by differential precipitation at various temperatures. The serums of group A give a marked reaction with the nonspecific antigen. They also form relatively less precipitate at 37 C. than do serums of group B. The chemical method has the distinct advantage that it eliminates arbitrary standards, since a quantity of antibody protein is directly referable from serum of one type to another. STOESSER, Minneapolis.

COMPARATIVE STUDIES ON THE PURIFICATION OF TETANUS AND DIPHTHERIA TOXINS. M. D. EATON and A. GRONAU, J. Bact. **36**:423 (Oct.) 1938.

Eaton and Gronau describe a simplified method for the purification of diphtheria and tetanus toxins by precipitation with cadmium chloride. The preparations of the two toxins, purified to about the same degree (separation of over 99 per cent of nitrogenous impurities), differ in the proportions of protein and nonprotein nitrogen present. Although purified diphtheria toxin is precipitated by a variety of protein reagents, purified tetanus toxin is not precipitable by acid or alum. The findings indicate that tetanus toxin differs in its chemical properties from diphtheria toxin, which is a typical protein. STOESSER, Minneapolis.

STUDIES ON HAEMOLYTIC STREPTOCOCCI FROM HUMAN SOURCES: I. THE CULTURAL CHARACTERISTICS OF POTENTIALLY VIRULENT STRAINS. H. K. WARD and G. V. RUDD, Australian J. Exper. Biol. & M. Sc. **16**:181 (June) 1938.

A method of identifying various strains of streptococci is presented which is suitable for use in the ordinary routine of the laboratory. The growth characteristics of these organisms in serum broth medium and serum peptone agar are described and are used to differentiate virulent A strains from other types of organisms. The methods of preparation of the culture mediums, the colony characteristics of the various strains, and the correlation of the results obtained with the results obtained by other methods of identification, such as Lancefield's serologic test, are discussed in detail. GONCE, Madison, Wis.

CHEMOTHERAPY OF BACTERIAL INFECTIONS. L. WHITBY, Lancet **2**:1095 (Nov. 12) 1938.

Much work has been devoted to improving the parent substance sulfanilamide, with the object of increasing its efficiency, widening the range of bacterial diseases which it can influence and reducing its toxic but rarely fatal effects. Well over a thousand such compounds have been studied in Elberfeld, Germany, alone, where Domagk and his assistants brought out the original prontosil (4-sulfonamido-2'-4'-diaminoazobenzene hydrochloride).

The compounds that have excited interest are divided into three groups:

1. In this group substitution has been made in the amino group (sulfanilamide belongs in this group); the range of activity is approximately the same; there is activity against hemolytic streptococci of groups A, B and C but not against D and F, and against meningococci and gonococci but not against any type of pneumococcus except type III.

2. In this group one hydrogen atom of the sulfonamido group has been substituted (includes such products as dimethyldisulfanilamide ["Uleron"] and sulfapyridine ["M & B 693"]); the range of activity is increased to include at least the pneumococcus; there is also equal if not greater activity against bacteria affected by the first group.

3. The third group includes compounds of the sulfone type; the range of activity of these compounds includes the pneumococcus and the hemolytic streptococcus, but toxicity has rendered these compounds unsuitable for clinical trial.

The manner in which all these drugs exert their action has been the subject of wide study but is not entirely clear yet.

Whitby from his own studies is convinced that these drugs are not stimulants of the leukocytes. By inhibiting coccal multiplication they prevent toxic depression of the marrow from an overwhelming infection, but they leave the marrow unstimulated. Furthermore, a survey of his unpublished experiments confirms the now generally accepted hypothesis that these drugs are not specifically concerned with the immunity mechanism.

The fact that the drug is not instantly bactericidal or even instantly bacteriostatic ("lag" phenomenon) is also of interest. LANGMANN, New York.

THE PRECIPITIN TEST APPLIED TO MELBOURNE HEMOLYTIC STREPTOCOCCI. H. M. BUTLER, M. J. Australia **2**:501 (Sept. 24) 1938.

Butler reports the examination of 113 strains of hemolytic streptococci isolated in Melbourne from human sources. Both group precipitin and biochemical reactions were studied. With Lancefield's technic for the group precipitin test 25 strains could not be allotted with certainty to any one group. The majority of strains associated with severe infections were typical members of group A (Lancefield). GONCE, Madison, Wis.

Metabolism; Infant Feeding; Milk and Other Foods

A COMPARATIVE STUDY OF THE METABOLISM OF CERTAIN AMINO ACIDS, WITH SPECIAL REFERENCE TO RESPIRATORY EXCHANGE AND HEAT PRODUCTION. M. KRISS, J. Nutrition **17**:1 (Jan.) 1939.

Kriss made a comprehensive study of the metabolism of three amino acids, namely, glutamic acid, aminoacetic acid and alanine, using albino rats. He postulates that, owing to the greater quantity of urea formed from glycine, the production of energy is relatively low (64.53 to 67.54 per cent) as compared with that from glutamic acid (90.8 per cent). Because of the relatively large quantity of unchanged amino acid eliminated in the urine, the metabolism of alanine is also relatively low (65.68 per cent). Kriss states that glutamic acid was absorbed to

the extent of 95 per cent, while glycine and alanine were completely taken up. He calculated that 3 per cent of glutamic acid, 7 per cent of glycine and 29 per cent of alanine were excreted in the urine. Factors were determined for computing the respiratory exchange, and the heat production in the metabolism of each of the three amino acids closely correlated with the ratios of carbon to nitrogen in these acids.

The article is supplemented with several tables.

The abstractor suggests that this work of Kriss may be beneficial in further research on muscular dystrophies.

FREDEEN, Kansas City, Mo.

ON THE DIGESTIBILITY OF RAW POTATO STARCH IN MAN. J. M. BEAZELL, C. R. SCHMIDT and A. C. IVY, J. Nutrition **17**:77 (Jan.) 1939.

The authors state that the "fact that a given quantity of raw starch disappears during passage through the gastro-intestinal tract does not mean that all that has disappeared has been usefully digested and assimilated." With raw potato starch, they found that bacterial fermentation accounted for a major part of the starch that was lost. The basis for this study was their finding that raw potato starch in vitro was almost entirely refractory to the action of gastrointestinal enzymes, as opposed to an earlier report by Langworthy and Deuel (*J. Biol. Chem.* **42**:270, 1920) which was responsible for a statement that is sometimes found in textbooks that large quantities of raw starch can be digested and assimilated by man.

FREDEEN, Kansas City, Mo.

OBESITY. E. W. HANCOCK, Nebraska M. J. **23**:452 (Dec.) 1938.

Perhaps underweight has been overstressed and overweight understressed. The disadvantages of overweight have been almost completely ignored, and too often the obviously obese child has been pointed to as a splendid example of modern nutritional methods. The disadvantages of overweight are the possibility of diabetes, various undesirable orthopedic conditions such as pronated feet, Perthes' disease, knock knees and lumbar lordosis. There is a feeling that obesity increases the risk in surgical conditions, pneumonia and other medical crises. Finally, the social complications are obvious. Most exceptional children are overweight, but faulty social adjustments may waste or pervert their superior mental ability. Obvious and marked obesity demands treatment even in the absence of symptoms. The question of appearance deserves attention, particularly in the adolescent girl. The etiologic factors should be determined if possible. It is difficult many times to determine definitely the causes of obesity. Authorities are about equally divided in their claims as to whether the obesity is due to perversion of an internal secretion or to a too liberal diet. Examination of the methods of those differing in etiologic theories brings out the fact that their methods are largely the same. It is true that practically all overweight children eat too much. It is recommended that the diet be limited to about 1,000 calories per day. The author proposes to treat all such children similarly, using a carefully constructed diet and administering endocrine substances as an adjuvant, realizing that their use is entirely empirical in the present state of knowledge. The advice frequently given to maintain the present weight and allow the child to grow into it is too conservative. It is essential that the diet be complete and be properly supplemented with the necessary vitamins. Thyroid extract given in doses of ½ to 1 grain (0.03 to 0.06 Gm.) constitutes the endocrine treatment. The fact that most of these children take fair-sized doses of thyroid without showing symptoms is taken as evidence that the medication is needed regardless of the basal metabolic rate. Pituitary extracts are sometimes used. No untoward effects have been noted, and the results have been very satisfactory. A sample diet is appended.

HAMILTON, Omaha.

NEWER DEVELOPMENTS IN CHILD NUTRITION. P. C. JEANS, Nebraska M. J. **24**:92 (March) 1939.

While there are various factors concerned in growth and health, nutrition is the most controllable. In selecting foods preference and instinct are too often the only guides. Intelligent understanding of the requirements of a good diet is a better criterion. Knowledge of the essential amino acids, minerals and vitamins is necessary. It was not until 1911 that a vitamin became known—vitamin C. Five years later fat-soluble A and water-soluble B were recognized. It was not until 1919 that it was definitely established that scurvy was due to a dietary deficiency. In 1922 vitamin D was distinguished from vitamin A, and a little later vitamin E became known. The complexity of vitamin B was established in 1925. It has not been many years since neither orange juice nor cod liver oil was given as a routine to babies, nor is it so very long ago that the tomato was considered poisonous. Survival of a human being or of a race is no criterion that the diet has been good.

A rational diet produces more rapid growth. It is desirable to recognize that there are other goals in nutrition than increases in height and weight—for instance, a healthy condition of the teeth, a satisfactory amount and condition of the musculature or of the bony framework, and efficient blood, all of which depend on nutritional factors. It is Jeans's belief that the diet of the average child is not entirely adequate. In his experience a child with active tooth decay who is placed in a hospital under close dietary supervision shows within two months or perhaps slightly more a complete arrest of caries. If it is granted that 70 to 80 per cent of children have tooth decay and if this is due to inadequate diet, it becomes obvious that a high proportion of children are not getting the diet they ought to have. If the diet is unsatisfactory from the point of view of tooth health, it is probably unsatisfactory from the point of view of other dietary objectives. The average American diet is built around bread, meat and potatoes—entirely satisfactory in some respects but inadequate as a complete diet. Protective foods—dairy products, fruits and vegetables—are necessary. The average American diet is deficient in calcium, vitamins A, B, D and to some extent G. All of these with the exception of D are relatively easily obtained in foods. Perhaps the first deficiency is calcium. The prejudice among physicians against milk is unjustified. It is the outstanding source of calcium. A quart of milk contains from four to six times as much calcium as all the rest of the child's daily diet put together. The child needs a gram of calcium a day. At least one and one-half pints of milk are required daily. Another dietary essential of which there is likely to be a deficiency is vitamin A, not because there is a deficiency of this vitamin in foods but because the foods containing it are not consumed. If a child is deficient in vitamin A, the chances are great that he is deficient in a great many other things because of his dietary habits. The problem of vitamin B is much the same as that of vitamin A. Vitamin B is widely distributed in common foods, and the same general diet which protects against deficiency of vitamin A is likely to protect against deficiency of Vitamin B. Of vitamin D there is a meager supply in foods. Egg yolk, milk and butter are said to contain vitamin D, but with ordinary methods of feeding hens and cows these sources contain so little that one can ignore them. The child needs vitamin D at all ages and during all periods of growth. A teaspoonful of cod liver oil or its equivalent is a satisfactory dose throughout the period of growth, except possibly for the premature baby. Strange enough it seems that babies who get around 400 units of vitamin D daily grow at a greater rate than those who get more. Those who get 1,500 units or more have a poorer appetite, and the growth response is less.

HAMILTON, Omaha.

A BOY AGED 4 YEARS WEIGHING TEN POUNDS. S. T. FALLA, Proc. Roy. Soc. Med. **32**:93 (Dec.) 1938.

The patient was a twin. The other twin was a girl. She weighed 34 pounds (15.4 Kg.) and was normally developed. The patient was normal until the sixth

week, when he suddenly commenced to vomit. Thereafter he was fed only brandy and water until he was 8 months old. When he was admitted to the hospital he was over 3 years old and weighed 10½ pounds (4.7 Kg.). He said a few words and understood what was said to him. He appeared to have insufficient saliva to masticate solid food. The results of the physical examination and of other investigations and the treatment are given in the report. The report is accompanied by pictures of the patient and his twin sister. WILLIAMSON, New Orleans.

NITROGEN METABOLISM AND UTILIZATION OF FOODSTUFFS IN CHILDREN RECEIVING DIETS CONTAINING VEGETABLE PROTEIN. A. BIEBER, Riv. di clin. pediat. **36**:961 (Nov.) 1938.

Two comparable diets were fed to infants from 2 to 9 months of age. One diet consisted of cow's milk, cereal water and sugar, and the other, of cow's milk, alfea flour, water and sugar. With each of 8 subjects the nitrogen storage by the body was higher when the alfea flour was given. (Alfea flour is a product of vegetables [tomato, spinach, carrots], cereals [corn, barley, wheat] and milk and egg proteins.)

HIGGINS, Boston.

MECHANICAL EXTRACTION OF BREAST MILK. E. SCHTEINGART, Arch. de pediat. d. Uruguay **9**:574 (Sept.) 1938.

Schteingart reviews different methods for mechanical extraction of breast milk and emphasizes the electrical device. The one he employs can extract the milk of 16 breasts simultaneously. The advantages of and indications for this method are enumerated.

SCHLUTZ, Chicago.

ACIDOSIS IN INFANTS OF BOGOTA, COLOMBIA. C. TORRES, Bol. Soc. cubana de pediat. **10**:314 (June) 1938.

Torres describes a serious type of acidosis in infants of Bogota—about 2,500 feet (762 meters) above sea level—characterized by continuous vomiting, indigestion, fever, leukocytosis, polynucleosis, acetonuria and marked prostration. Children below 1 or 2 years of age are affected. The causes are not definitely known. The altitude (which may produce anoxemia), infections and excessive feedings are some of the factors offered in explanation of the condition.

SCHLUTZ, Chicago.

TREATMENT OF NURSLINGS' ATROPHY WITH EXTRACTS OF LIVER AND HYPOPHYSIS. A. VON SZASZ and S. VON GARDOS, Monatschr. f. Kinderh. **76**:322 (Dec.) 1938.

Reasoning from the fact that in children with severe malnutrition the liver diminishes in size and that some children show polyuria, the authors conclude that there must be involvement of the liver and of the posterior lobe of the pituitary. They have used preparations of these endocrine glands in the treatment of malnutrition. The usual good results are reported.

GERSTLEY, Chicago.

ROASTED SOYBEAN IN INFANT FEEDING. R. A. GUY and K. S. YEH, Chinese M. J. **54**:101 (Aug.) 1938.

This communication supplements an earlier one by the same authors (Soybean "Milk" as a Food for Young Infants, *Chinese M. J.* **54**:1 [July] 1938). It was found that soybeans roasted and ground and then emulsified in water make a safe, convenient and complete source of protein and vitamin B complex for infant feeding. By this method the protein content is accurately known. The preparation is palatable, and it contains all the known amino acids, salts and vitamins necessary for body development. In addition to the administration of this roasted flour, the

authors recommend the administration of sodium chloride, calcium lactate, cod liver oil and a soup made from cabbage. Guy and Yeh describe the method of feeding the mixture and report 2 typical cases from the series of 49 observed.

NEFF, Kansas City, Mo.

EXTRACELLULAR AND INTRACELLULAR FLUID. A. KROGH, Acta med. Scandinav. (supp.) **96**:9, 1938.

Krogh found the thiocyanate method of Bourdillou satisfactory for determining extracellular and intracellular fluid in rabbits. The extracellular fluid was found to be 26 per cent of the total weight in the 2 animals in which it was determined.

KAJDI, Baltimore.

Vitamins; Avitaminoses

CLINICAL SIGNIFICANCE AND ESTIMATION OF BLOOD VITAMIN B_1. E. N. ROWLANDS and J. F. WILKINSON, Brit. M. J. **2**:878 (Oct. 29) 1938.

This article does not lend itself to abstracting. It must be read in its entirety to be properly evaluated.

ROYSTER, University, Va.

OBSERVATIONS ON THE RELATION OF LEUCOCYTOSIS TO ASCORBIC ACID REQUIREMENTS. T. D. CUTTLE, Quart. J. Med. **7**:575 (Oct.) 1938.

Cuttle studied the vitamin C requirements in 4 cases of leukemia and in 6 controls. The criteria used were: (1) maintenance of a "minimal standard excretion" of the vitamin, (2) response to a test dose of ascorbic acid, (3) amount of ascorbic acid required to produce saturation and (4) levels of ascorbic acid in blood and serum.

From the data he obtained by testing these aspects of the vitamin C requirements Cuttle concluded that in leukemia an excessive amount of ascorbic acid can be absorbed and retained and that its value within the blood cells is increased. These abnormalities bear a direct relation to the number of circulating leukocytes. It is suggested that leukocytes absorb a large amount of ascorbic acid.

He suggests also that the increased requirements for vitamin C in infection are probably partially due to the resultant leukocytosis.

BRADFORD, Rochester, N. Y.

NEWER ASPECTS OF THE NERVOUS DISORDERS IN AVITAMINOSIS. H. M. ZIMMERMAN, Confinia neurol. **1**:6, 1938.

Zimmerman evaluates the role played by vitamins in the production of nervous disorders. Lack of these food factors not only leads to the development of beriberi and pellagra but is responsible for a large number of allied conditions, such as the polyneuritis and pellagroid manifestations of chronic alcoholism and the so-called cachectic polyneuritis. In this group should also be included the polyneuritis of diabetes and of the pernicious vomiting of pregnancy and that associated with the gastrointestinal and hepatic lesions produced by metallic poisons, such as arsenic and phosphorus.

The vitamins which are responsible for the maintenance of a healthy nervous system in man are vitamins B (B_1) and G (B_2), the former being the heat-labile antineuritic factor which prevents beriberi and the latter the thermostabile substance which appears to prevent pellagra. Experiments have indicated also that vitamin A is important in the preservation of an intact nervous system, and it has been suggested that this is true also of vitamins C and D.

Deficiency of vitamin B (B_1) is known to cause typical beriberi, characterized by noninflammatory demyelination of the peripheral nerves, usually involving first

the lower extremities. These changes have been produced in experimental animals which have been fed diets deficient in vitamin B (B_1). The resulting anatomic changes are as follows: Extensive demyelination of the peripheral nerves and destruction of axis-cylinders in animals with chronic deficiency. There are no changes in the spinal cord. The peripheral neuritis of chronic alcoholism, of pernicious vomiting of pregnancy, of diabetes mellitus and of other organic diseases suggests that these conditions are closely related to beriberi.

Pellagra in man and its analogue black tongue in dogs result from a deficiency in vitamin G (B_2). In these conditions there are not only marked destruction of the medullary sheaths of the peripheral nerves but also degeneration of the medullary sheaths with resulting gliosis in the posterior columns of the spinal cord, slight changes in the other fiber tracts of the cord and degeneration of the medullary sheaths of the posterior, and less often the anterior, nerve roots of the cord. Clinical pellagra may also occur in association with chronic alcoholism and various debilitating diseases. The lesions of the spinal cord associated with pernicious anemia resemble in many respects those in pellagra and in experimental G avitaminosis, but it is not yet proved that vitamin deficiency can cause this combined system involvement or that administration of vitamins will ameliorate the symptoms. De Jong, Ann Arbor, Mich. [Arch. Neurol. & Psychiat.]

Hypervitaminosis A. V. Baptista, J. de pediat. **5**:7 (Aug.-Oct.) 1938.

The question of a hypervitaminosis A is raised, with the author's belief that the condition is of no clinical importance since there has been no proof of its harmfulness in human beings. However, a thorough and interesting review of the subject from the experimetal point of view is carried out. According to this review the conclusions drawn favor the opinion of most of the investigators who had demonstrated the toxicity of large doses of this vitamin in lower animals. The importance of a synergistic action with the other vitamins is commented on by the author, who quotes the works of European as well as American authors to show this.

It is finally deduced that in the case of vitamin A, as in that of vitamin D, it is safe to use even large doses in man. Soto, Habana, Cuba.

Scurvy and Vitamin C. O. Lustosa, J. de pediat. **5**:17 (Aug.-Oct.) 1938.

A child 15 months old is studied and presented as showing typical scurvy. Nothing of particular interest is offered other than some comments on the latest investigations of vitamin C in relation to scurvy. Soto, Habana, Cuba.

Moeller-Barlow Disease. C. Urrutia, Rev. chilena de pediat. **9**:768 (Sept.) 1938.

A case of atypical scurvy is described. Scurvy is now rare in Chile in spite of the poverty of the masses, a fact attributed to the better understanding of diets. This improvement has increased the number of cases of mild or atypical scurvy, the diagnosis of which is difficult and the treatment of which is therefore often inadequate. Schlutz, Chicago.

Vitamin Therapy. R. Boller, Wien. klin. Wchnschr. **51**:366 (March 25) 1938.

According to Boller, the sphere of vitamin therapy has been broadened in recent years, especially in internal medicine. Vitamins are now prescribed not only for avitaminoses and hypovitaminoses but also for many other illnesses which have nothing to do with the diseases due to lack of vitamins.

First, however, with regard to avitaminoses and hypovitaminoses (which may be due either to lack or to insufficient resorption of vitamins), the author cites

certain types which have been found with some frequency in Germany. B_1 avitaminosis in adults has been found to be caused by alcoholism. It may take the form of polyneuritis or of a pellagra-like condition. Less often certain primary avitaminoses are encountered. These include the lack of vitamin A in underfed persons, especially at the end of winter; the lack of vitamin C in persons in whose diets there have been no fresh vegetables or fruit; the lack of B_1 (frequently observed during the World War), which causes the so-called hunger or war edema. True beriberi, however, is rarely found in Europe.

With regard to their therapeutic value, the author catalogues the vitamins as follows:

1. Vitamin A—the "epithelium-protecting" vitamin. It has been found useful in treating slowly healing wounds (e. g., ulcera cruris), diabetic gangrene and gastric and duodenal ulcers. In treating ulcers of the stomach injections of vitamin A have been successful, without any dietary prohibitions being required. Exophthalmic goiter and certain forms of gastritis have also responded to vitamin A. In cases of inoperable carcinoma loss of strength may be prevented for several months beyond the usual time by administration of vitamin A.

Vitamin B_1, the "neurologic" vitamin. Its widest application has been in the treatment of nervous diseases. In disturbances of the spinal cord it has a favorable effect on the peripheral nerve symptoms. It promises to be of value in treating postdiphtheritic paralysis, amyotrophic lateral sclerosis and even multiple sclerosis. Besides its neurologic influence, vitamin B_1 is effective in pernicious anemia, funicular myelosis and cardiac conditions. In some cases of diabetes mellitus it increases susceptibility to insulin.

Vitamin B_2, riboflavin. No B_2 avitaminosis has been noted in man, but B_2 is required for proper growth.

Vitamin B_6, the P-P factor. This is believed to be identical with the pellagra-preventing element.

Vitamins B_2, B_6 and Castle's extrinsic factor are sometimes known as the vitamin B_2 complex. The therapeutic use of the B_2 complex is many sided. It cures conditions of the tongue and oral membrane. Pellagra and sprue respond to a diet rich in the complex. Severe diarrheas, of course, may prevent necessary resorption of the vitamin. Tropical anemia and leprosy have also been reported as being due to lack of B_2 complex.

Vitamin C, the antiscorbutic vitamin. Vitamin C is a specific for scurvy. It is also antihemorrhagic, being a good hemostyptic not only in hemorrhagic diatheses but also in various diseases with a tendency toward bleeding. Caries, gingivitis, alveolar pyorrhea and disturbances of growth are among the many conditions in the therapy of which vitamin C has been used to advantage. Recently, it has been tried in the treatment of malignant diphtheria.

Vitamin D, the antirachitic vitamin. Primarily the specific therapeutic agent against rickets, it is also used in osteomalacia. Small doses have been found helpful in cases of pulmonary tuberculosis, but demineralization may result from massive doses. Certain allergic diseases also have been successfully treated with vitamin D.

Vitamins E, H, I and K are still moot factors. ABT, Chicago.

TREATMENT OF NUTRITIONAL DISORDERS IN INFANTS WITH ASCORBIC ACID. E. URBANITZKY, Ztschr. f. Kinderh. **59**:553 (April 2) 1938.

Urbanitszky reports that good results were obtained in the treatment of diarrhea with ascorbic acid when this was given intravenously. When it was given subcutaneously or intramuscularly, recovery was slow. Negative results following oral administration may be ascribable to a disturbance in absorption. Furthermore, Schroeder and Einhauser were able to show that vitamin C is destroyed by pathologic intestinal flora. SIEMSEN, Chicago.

VITAMIN E: ITS INFLUENCE ON THE LACTATION OF MOTHERS AND THE GROWTH OF THEIR CHILDREN. G. GAEDKE and C. BENNHOLDT-THOMSEN, Ztschr. f. Kinderh. **60**:52, 1938.

Since Evans and Burr discovered vitamin E as an antisterility factor, various other functions have been reported for the vitamin. There are two possible modes of action of this vitamin: 1. It may influence the glands of internal secretion. 2. It may influence the metabolism of iron and manganese.

Vitamin E in excess of requirements is excreted. Its excretion in breast milk has been demonstrated.

The authors studied the influence of vitamin E supplements on 6 lactating mothers (2 serving as controls) and on the growth of their infants. The observations extended over many months. Periods in which vitamin E supplements were given were alternated with periods in which the supplements were omitted. The quantity of milk secreted and the fat content were not increased. An interesting incidental finding was that, although the quantity of milk fluctuated, the amount of fat secreted remained constant. The effects of vitamin E supplements on the increments in weight and length of the infants were likewise negative. The negative results should not be interpreted as indicating a lack of effect of vitamin E on lactation and on the growth of the infants but as indicating that the ordinary diet is adequate in vitamin E.

Young rabbits fed large amounts of vitamin E tolerated the oil poorly as compared with rabbits fed olive oil, and no stimulation of growth was observed.

SIEMSEN, Chicago.

RECENT CONCEPTIONS OF VITAMIN ACTIVITY. Z. KOLODZIEJSKA, Pediatria polska **18**:165 (March) 1938.

In biology no other branch has been so extensively developed as that on vitamins. The author reviews scientific research on vitamins and gives formulas. In conclusion she states that the action of vitamins depends on many factors, particularly the condition of the gastrointestinal tract. Therefore any proof of vitamin activity should be accepted with caution at the present time.

KRUPINSKI, Chicago.

NEW KNOWLEDGE ON THE RELATION OF LIVER FUNCTION TO VITAMIN B_1. Y. HIRATO, Orient. J. Dis. Infants **23**:23 (May) 1938.

Experiments were made on rabbits. The observations were as follows: The marked decrease in hepatic glycogen resulting from injury to the parenchyma of the liver can be reversed by administration of vitamin B_1. The normal liver's store of glycogen can be increased by the same method. The disturbance of liver function produced by excessive sugar feeding can be completely amended by treatment with vitamin B_1. Histologically, the degeneration of the liver cells produced by parenchymatous poisons can be demonstrated to undergo reversal under vitamin B_1 therapy. On the basis of the foregoing evidence it is stated that vitamin B_1 may be regarded as a completely effective detoxicating agent for the injured liver.

KATO, Chicago.

INFLUENCE OF VITAMIN B_1 AND VITAMIN C ON ANAPHYLACTIC SHOCK. M. YAMAMOTO, Orient. J. Dis. Infants **23**:233 (March) 1938.

The neutralizing effect of vitamin B_1 and of vitamin C on the development of anaphylactic shock in the guinea pig sensitized to horse serum was studied by the Schultz-Dale uterine strip method. If crystalline vitamin B_1, in doses of 0.25 mg., was administered to the animal either before the injection of sensitizing serum or during the period of incubation or even as late as several hours before the

examination, definite neutralization or even checking of the anaphylactic shock could be demonstrated. It is believed by the author that this action was due to an effect on the function of the liver such that the formation of antibodies was prevented.

Likewise when 100 mg. of pure vitamin C was injected either before the administration of the sensitizing horse serum or several hours before the examination, the development of anaphylactic shock was checked, but if this dose was injected during the period of incubation the appearance of allergic phenomena was accelerated. This is explained by the author as being due to the fact that during the period of incubation the allergen has already reached its maximum penetration into the tissues, while at other periods the vitamin prevents the antigen from invading the tissues, thereby promoting its elimination from the body.

A combination of vitamins B_1 and C produces the greatest neutralizing effect on the allergic phenomenon. These observations led the authors to suggest that the combined use of vitamins B_1 and C was the best method of treating allergic patients.

KATO, Chicago.

ADMINISTRATION OF VITAMIN C IN THE FORM OF ASCORBIC ACID AND OF FRUIT JUICE. S. M. SJAMSOEDIN, Maandschr. v. kindergeneesk. **8**:76 (Nov.) 1938.

Experiments in which guinea pigs were put on a vitamin C–free diet, to which in some experiments tomato juice and in some others ascorbic acid had been added, showed that the influence of tomato juice on the growth of the animals was more favorable than that of ascorbic acid. The author concludes from his experiments that 0.5 mg. of vitamin C in the form of tomato juice effects a better result than 0.75 mg. of the same vitamin in the form of ascorbic acid. When both supplements were given in excessive quantities, no difference in their respective effects on growth could be noticed.

VAN CREVELD, Amsterdam, Netherlands.

Prematurity and Congenital Deformities

MONSTROSITY FOLLOWING THE BIRTH OF NINE NORMAL CHILDREN. A. I. WEISMAN, Arch. Pediat. **55**:448 (July) 1938.

A case is reported.

ORR, Buffalo.

A SYNDROME OF INFANTILISM, CONGENITAL WEBBED NECK, AND CUBITUS VALGUS. H. H. TURNER, Endocrinology **23**:566 (Nov.) 1938.

A hitherto unreported syndrome—infantilism, webbing of the skin of the neck and deformity of the elbow (cubitus vulgus)—is described as observed in 7 adolescent girls, and an addendum notes that since the paper was written the author has seen the syndrome in 3 other persons. There was evidence also of delayed union of the epiphyses.

Treatment with an extract of the anterior lobe of the pituitary containing growth hormone was unsatisfactory; there was definite genital development following administration of an extract of anterior lobe of the pituitary containing gonadotropic hormone in the 2 patients treated.

JACOBSEN, Buffalo.

THE PREMATURE INFANT—EARLY GENERAL AND FEEDING CARE. J. H. HESS, Illinois M. J. **74**:506 (Dec.) 1938.

This excellent article is too comprehensive and detailed to be abstracted adequately. Its authoritative contents are well worth one's thorough perusal.

BARBOUR, Peoria, Ill.

DEVELOPMENTAL ABBREVIATION OF TERMINAL PHALANGES. H. J. BURROWS, Brit. J. Radiol. **11**:165 (March) 1938.

This is a hereditary shortening of the terminal phalanges of the thumbs or great toes and sometimes of the first or second fingers. It has been found in 1.5 per cent of cases examined. The condition is bilateral twice as frequently as unilateral. Apparently in none of the cases has it been discovered before the age of 5. Normally the terminal phalanx is to the middle phalanx as 0.75 is to 1; a pathologic ratio is 0.4 to 1. The cause of the premature fusion and lack of development of the phalanges involved has not been determined.

SQUIRE, Chicago.

DUPLICATION OF THE HIND-END OF AN ANENCEPHALIC FOETUS. A. E. HARBESON, J. Obst. & Gynaec. Brit. Emp. **45**:810 (Oct.) 1938.

An anencephalic monster with multiple additional malformations is described. Most notable of these were a duplication of the spine below the tenth thoracic vertebra together with a duplication of the appendix, large bowel and anus. There were also two separate unicornuate uteri, each with a separate vagina and vaginal orifice. Only two ovaries were present.

POTTER, Chicago.

A FLYING FOETUS. R. W. KNOWLTON, J. Obst. & Gynaec. Brit. Emp. **45**:834 (Oct.) 1938.

An infant is described whose intrauterine position consisted of a fully extended head lying to the right in the fundus, while the body was in a peculiar flying attitude, with the back extended in the position of opisthotonos and the legs overextended at the hips with knees flexed. This position was assumed for several weeks after delivery, but the infant when seen at the age of 4 months was normal. Delivery was by cesarean section.

POTTER, Chicago.

CRANIOFACIAL DYSOSTOSIS. A. GAREISO, J. E. VIVIANI and A. M. CERDEIRO, Rev. méd. latino-am. **23**:1245 (Aug.) 1938.

In 1912 Cruzon in France described a form of osseous dystrophy involving primarily the cranium, characterized by brachycephaly, asymmetry of the head and face, prominence of the metopic suture, hypoplasia of the superior maxilla, exophthalmos and mental deficiency, which he called hereditary craniofacial dysostosis. Since that time cases have been reported in which certain variations from the classic Cruzon syndrome were observed, depending on the sutures involved. This developmental defect has its origin in premature synostosis of certain sutures, with involvement of the metopic, sagittal, coronal and lambdoid sutures, resulting in trigonocephaly, scaphocephaly and acrocephaly, respectively. The syndrome resembles acrocephalosyndactylism (Apert's disease).

The authors describe a case of Cruzon's disease in a girl aged 10 years, whose father presented the same malformations. A case of Apert's disease in a girl of 10 years is also described to bring out the similarity between the two conditions.

DWYER, Kansas City, Mo.

FETAL PERITONITIS. V. WAGNER, Časop. lék. česk. **75**:1591 (Dec. 4) 1936.

A review of the literature is followed by a report of a case. An infant 3 days old was operated on because of signs of diffuse peritonitis. The peritoneum was markedly thickened; the loops of bowel had firm fibrous adhesions; meconium was present, and, in addition, there was an inflammatory reaction about the necrotic cecum and ileum as well as stenosis in the region of the ileocecal (Bauhin's) valve. The perforation was not found, but the healed-over focus with inclusions of lanugo speaks for a fairly recent perforation.

STULIK, Chicago.

HYPERTELORISM (GREIG). K. BOJLEN and T. BREMS, Acta path. et microbiol. Scandinav. **15**:217, 1938.

Since 1924, when Greig described the condition of ocular hypertelorism, 42 cases purporting to be instances of this anomaly have been reported. On critical analysis of the reports it is found that only 27 of the 42 cases may be taken with a fair degree of certainty to be cases of hypertelorism in the sense defined by Greig. Some of the errors in diagnosis are attributable to the difficulty of differentiating between this anomaly and other malformations that may be associated with great breadth between the eyes (congenital facial or nasal clefts, tumor formation over the root of the nose, Apert's and Crouzon's cranial dysostoses).

On the basis of these 27 rather well established cases of hypertelorism and the cases recorded in the present article, a review is given of the symptom complex of this deformity (the question of defective intelligence, the physiognomic characteristics and the combination with other deformities and diseases). As to the mental defect in particular, this is by no means a constant feature of the symptom complex, even though the combination of hypertelorism and mental defect probably occurs too often to be considered an accidental coincidence.

Familial hypertelorism is not recognized generally to occur. In this paper mention is made of 11 cases among 24 members of the same genealogical tree. Five generations showed the hypertelorism as a hereditary deformity, transmitted as a dominant character. So in these cases the question of heredity is elucidated fully.

As to the causes and pathogenesis, the cases reported here furnish no evidence in support of new views. It is a question whether hypertelorism represents a primary disturbance of the development of the bones that may be accompanied by disturbances of the development of the brain, or whether it represents a primary disturbance of the development of the brain that needs not result in mental defect. The hereditary appearance of the deformity in the authors' cases suggests that the primary factor might be looked for in an anomalous development of the prosencephalon.

FROM AUTHORS' SUMMARY. [ARCH. PATH.]

Newborn

RELATIVE VALUE OF PURE OXYGEN AND OF CARBON DIOXIDE MIXTURES IN EXPERIMENTAL RESUSCITATION. N. J. EASTMAN, R. B. DUNN and J. KREISELMAN, Am. J. Obst. & Gynec. **36**:571 (Oct.) 1938.

Experimental anoxemia in animals presented the clinical picture of asphyxia neonatorum. Resuscitation in the experimental animals was accomplished just as quickly by insufflation of pure oxygen as by insufflation of carbon dioxide mixtures, and in profound asphyxia pure oxygen was found to be more efficacious than carbon dioxide. Following resuscitation with pure oxygen the respiration became normal in rate, amplitude and general character, but after resuscitation with carbon dioxide mixtures the respiration tended to be convulsive and irregular and frequently became shallow, requiring further artificial respiration.

ARENA, Durham, N. C.

PLACENTAL INTERCHANGE: II. COMPARISON OF THE TOTAL BASE CONCENTRATION OF THE FETAL AND MATERNAL BLOOD AT PARTURITION. H. E. THOMPSON JR. and W. T. POMMERENKE, J. Clin. Investigation **17**:609 (Sept.) 1938.

Studies were made of the venous plasma of 30 parturient women and of the venous and arterial plasma from the umbilical cord blood of their respective newborn infants. The total base in the blood plasma was determined by Key's method. The mean total base per liter of maternal plasma was found to be 144.6 ± 2.5 milliequivalents; that of infant arterial plasma, 147.5 ± 3.5 milliequivalents; that of infant venous plasma, 146.8 ± 3.2 milliequivalents. The mean

difference between maternal and infant arterial plasma was 2.2 milliequivalents. The differences between the mean venous and arterial values for the blood of infants were less than the experimental error.

GUEST, Cincinnati.

MENINGEAL HEMORRHAGES OF THE NEWBORN. M. RIVIÈRE, J. de méd. de Bordeaux **114**:129, 1937.

Rivière discusses the meningeal and ventricular hemorrhages which, because of their anatomic importance, may give rise to clinical symptoms. He disregards the microscopic meningeal hemorrhages, which, according to Tassovatz, occur in 95 of 100 normal deliveries. The incidence of meningeal hemorrhages that cause clinical symptoms has been estimated differently by various authors. Whereas Waitz judged it to be 11 per cent, Tassovatz estimated it at 0.05 per cent. In summarizing his observations, Rivière says that their incidence may be fixed at about 1 in 100 cases. The etiologic factors are dominated, on the one hand, by syphilis and prematurity, often concurrent, and, on the other, by obstetric traumatism. The etiologic responsibility is about equally divided between the predisposing factors (syphilis and prematurity) and the trauma. There are four chief mechanisms: (1) intracranial venous hypertension of circulatory origin; (2) sudden thrusts of the cerebrospinal fluid in the arachnoid spaces; (3) ruptured vessels in the cerebellar tentorium, and (4) in exceptional cases, direct vascular lesions by pieces of bone. The symptoms differ according to circumstances. There may be real or apparent death or atypical symptoms of muscular hypertension with attacks and clonic convulsions. The cortical and bulbar centers may be inhibited or irritated by a subdural hematoma. The ventricular hemorrhages become manifest by stupor; the signs of cortical irritation do not appear until later. The clinical diagnosis can always be corroborated by lumbar, suboccipital or ventricular puncture. The immediate prognosis is grave in that the mortality exceeds 35 per cent. The late prognosis is indefinite if suitable treatment has not been employed, for a large number of encephalopathies derive from intrapartum meningeal hemorrhages. The prophylactic treatment should ameliorate the predisposing factors by combating syphilis and prematurity and should make efforts to reduce or suppress the obstetric traumatism by careful choice of interventions. The curative treatment should decompress the centers by lumbar, suboccipital or ventricular punctures. These should be repeated as often as signs of intracranial hypertension exist. Hemostasis is produced by assuring the normal play of respiration and by injections of hemostatic serum or of maternal blood. This treatment, which relieves the cortex of the compressive and destructive action of the subdural hematoma, seems to improve greatly the late prognosis of the meningeal hemorrhages of the newborn.

J. A. M. A.

BIOMETRIC DATA ON THE NEWBORN OF THE PROVINCE OF PERUGIA. A. PICCIOLI, Lattante **9**:407 (Oct.) 1938.

Data on the weight and height of 2,951 newborn infants from Perugia are presented. The arithmetic mean weight was 3.384 Kg. for boys; 3.204 Kg. for girls; 3.255 Kg. for infants of primipara and 3.334 Kg. for infants of multipara. The arithmetic mean length was 50.39 cm. In size the Perugian newborn is quite comparable with the newborn of other Italian provinces.

HIGGINS, Boston.

ERYTHROCYTOMETRIC FORMULA, NUMBER OF RED CELLS AND OF RETICULOCYTES IN THE NEWBORN AND THEIR VARIATION IN NUMBER IN THE FIRST DAYS OF LIFE. F. RASI and M. BOLLETTI, Riv. di clin. pediat. **36**:605 (July) 1938.

Studies were made on the blood of 16 infants at birth and at intervals thereafter up to two months. At birth the average size of the red cell is above the

normal for adults and children; it increases to a maximum size at twenty-four hours and then gradually falls to the normal in from fifteen to thirty days. Marked anisocytosis is present at birth, increases for twenty-four hours and then gradually diminishes over a period of two months. The number of red blood cells at birth is about 5,000,000; the number increases to 6,000,000 to 7,000,000 in twenty-four hours and falls to normal in about fifteen days. The percentage of reticulocytes increases from 2 to 7 in the first twenty-four hours of life and then gradually falls to normal.

These changes in the red cells are believed to be due to a regenerative stimulation of the bone marrow caused by the change from intrauterine to extrauterine life and by the asphyxia of childbirth.

HIGGINS, Boston.

COMPLEMENT IN NEWBORN CHILDREN, IN INFANTS AND IN FETUSES. P. SÖLLING, Ztschr. f. Immunitätsforsch. u. exper. Therap. **91**:15, 1937.

The titer of the complement varied little with adults. Very marked deviations in either direction were remarkably rare. Low values appeared more frequent with syphilitic persons. With 20 infants (first year of life) the values were almost the same as with adults and were only slightly higher than those with 93 mature newborn children. With 28 fetuses the values differed according to the age. Complement was detectable from the fourteenth week on but was quite weak until the twenty-eighth week, after which the titers came close to those of mature newborn children.

DAVIDSOHN, Chicago. [ARCH. PATH.]

Acute Contagious Diseases

A STUDY OF THE TYPES OF CORYNEBACTERIUM DIPHTHERIAE. N. HIRSHBERG, Arch. Pediat. **55**:710 (Nov.) 1938.

One hundred and eighty-six strains of Corynebacterium diphtheriae were studied—66 from clinical cases, 22 from carriers and 100 from unknown sources in the Chicago area. The strains could usually be classified as gravis, mitis or intermedius; a large number showed variable characteristics. Virulence was not dependent on the type of strain. Persons of the same family, whether carriers or patients, were found to harbor strains of the same type. A study of the types of C. diphtheriae may be useful in studying the epidemiology of diphtheria.

ORR, Buffalo.

PROBLEMS RELATING TO VACCINATION OF THE NEWBORN. L. O. TRAVIS, Arch. Pediat. **55**:782 (Aug.) 1938.

Routine vaccination of newborn infants may be safely and satisfactorily performed by using a potent virus and a traumatizing technic. It should be done whenever necessary; for example, when there is an epidemic of smallpox in a community in which the proportion of the population vaccinated is low or when the situation is such that the child cannot or probably will not return for vaccination at a later date. Otherwise, the optimal age for primary vaccination seems to be from 3 to 6 months.

ORR, Buffalo.

WHY DO NOT MORE CHILDREN GET MILK-BORNE INFECTIONS? Health News **15**:122 (July 18) 1938.

The study of milk-borne epidemics shows that both adults and children consume about the same amount of milk per capita but that the milk fed to children is usually heated, giving partial protection against infection.

AIKMAN, Rochester, N. Y.

RECENT OUTBREAKS OF COMMUNICABLE DISEASES. Health News **15**:134 (Aug. 8) 1938.

An epidemic of 13 cases of typhoid fever is reported in a village. It was found to be due to consumption of infected raw milk.

An outbreak of gastroenteritis occurred in a children's camp in July 1938, affecting 50 children. The source of infection was found to be water obtained from a newly dug well.

AIKMAN, Rochester, N. Y.

DIPHTHERIA PREVENTION. Health News **16**:46 (March 20) 1939.

Of 68 cities, 51 have reported 35 per cent or more of children under 5 years of age immunized against diphtheria. Three cities have reported 95 per cent immunized. In New York state exclusive of New York city, in 1938, 163 cases of diphtheria were reported, establishing a new all time low morbidity record. The importance of immunization of children under 5 years of age is stressed.

AIKMAN, Rochester, N. Y.

INTRADERMIC IMMUNIZATION AGAINST SCARLET FEVER. C. A. EARLE, Illinois M. J. **74**:248 (Sept.) 1938.

Earle relates his experiences with intradermic injections of scarlatinal toxin. The results were more satisfactory than those obtained with subcutaneaus injections. He strongly advocates immunization of all susceptible children.

BARBOUR, Peoria, Ill.

EOSINOPHILIC BODIES IN THE BLOOD OF MUMPS. H. H. PARSONS, Mil. Surgeon **83**:541 (Dec.) 1938.

When eosin-stained red blood cells were counterstained with acid fuchsin, 125 persons with mumps showed eosinophilic bodies in these cells at least one day before the parotid glands began to swell and from sixteen to seventeen days thereafter. These bodies were found in approximately every sixth blood cell. Complications, such as orchitis or meningoencephalitis, seemed to increase the numbers in the blood.

SANFORD, Chicago.

PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **53**:2075 (Nov. 25) 1938.

For the period of Oct. 9 to Nov. 5, 1938, the incidence of influenza increased about 45 per cent (3,836 cases). The incidence of measles was also slightly above the median prevalence. The incidence of poliomyelitis, smallpox, typhoid, meningitis and scarlet fever, respectively, was below median. The mortality was 10.8 per thousand, which is average.

SANFORD, Chicago.

MENINGOCOCCUS MENINGITIS. T. C. SMITH, W. T. MAXSON and D. F. H. MURPHEY, South. M. J. **31**:1168 (Nov.) 1938.

The mortality rate for the group studied was 35.6 per cent. A review of the old and recent mortality rates for meningitis suggests that in general treatment has not been efficacious or that the serum has been lacking in potency. From their experiences with this group of cases the authors claim that there is no advantage in introducing serum into the subarachnoid spaces. Intravenous administration of large doses of antitoxin seems to be as beneficial as intrathecal therapy, and, in addition, it is more comfortable for the patient. Sulfanilamide seems to be a valuable adjunct in the treatment of this disease.

The prognosis for a patient with absence of encephalitic symptoms and a low spinal fluid cell count is extremely good.

SCHLUTZ, Chicago.

EARLY TREATMENT OF POLIOMYELITIS. J. H. CHARBONNEAU, Union méd. du Canada **67**:719 (July) 1938.

Charbonneau summarizes the commonly accepted methods of treatment of poliomyelitis. Complete rest in bed, with early orthopedic attention, is required in every case. Serum therapy is advocated in many European countries, and, he feels, as long as there is any possibility of its being efficacious, it should be given. It must, however, be administered early, and in doses of 25 to 100 cc. Repeated lumbar punctures or injections of hypertonic solutions may be used. Diathermy treatment of the cord is probably of no use. Respirator care is life saving in cases in which the muscles of respiration are involved but is useless in the pure bulbar type.

Individual precautions are probably sufficient to prevent spread to attendants. A mask should be worn when one is dealing with an uncooperative patient.

DAFFINEE, Boston.

THREE CASES OF ENCEPHALITIS WITH VARICELLA. P. JOSSERAND, Bull. Soc. de pédiat. de Paris **36**:207 (April) 1938.

Three children with varicella showed symptoms of encephalitis. It is stated that such symptoms are likely to be cerebellar, in contrast to the symptoms of encephalitis encountered with measles, which are usually cerebral. It would appear that postinfectious encephalitis is not the result of infection by one neurotropic virus but rather of infection with the virus responsible for the disease which is accompanied by encephalitis.

BENJAMIN, Montreal, Canada.

TREATMENT OF SEVERE VARICELLA WITH INJECTION OF CONVALESCENT BLOOD. J. PARAF and P. BOULANGER, Bull. Soc. de pédiat. de Paris **36**:214 (April) 1938.

A girl 6½ years old had severe varicella and was given 15 cc. of blood intramuscularly on the fourth day of the disease. This was obtained from a child who had had varicella fifteen days previously. The patient showed improvement the day after the injection, and her temperature returned to normal on the seventh day of illness. Although there have been conflicting reports concerning the efficacy of convalescent serum in the treatment of varicella, the serum was considered of benefit in this case.

BENJAMIN, Montreal, Canada.

UNILATERAL DEAFNESS FOLLOWING ANTIDIPHTHERITIC VACCINATION. F. CHAVANNE, Oto-rhino-laryng. internat. **26**:481 (Sept.) 1938.

Deafness from antityphoid inoculations has been observed previously by Chavanne. The present instance is recorded with the thought that it may be useful in some medicolegal case and to reenforce the advice that prophylactic treatment be suspended if the first or second injection is followed by an abnormal reaction.

The patient, aged 5 years, had severe reactions, consisting of headache, vomiting and fever, after each prophylactic injection of antidiphtheritic vaccine. The third injection was followed by deafness in the right ear. In the Weber test the sound was lateralized to the left; the Rinne test was negative on the right and positive on the left side, and hearing in the right ear was diminished for all tones. High tones were less well heard than low tones. Vestibular reactions were normal. The patient was observed in March 1928, at which time he was still deaf for the medium voice and whisper.

DENNIS, San Diego, Calif. [ARCH. OTOLARYNG.]

INFECTIOUS DISEASES IN 1938. C. DOPTER, Paris méd. **21**:461 (June 4) 1938.

This article contains brief reviews of the recent literature on typhoid, dysentery, undulant fever, plague, tularemia, spirochetosis icterohaemorrhagica, measles, scarlet

fever, smallpox, vaccination, mumps, infections by the staphylococcus, streptococcus, pneumococcus, gonococcus and meningococcus, poliomyelitis, diphtheria, typhus, Rocky Mountain spotted fever, trachoma, yellow fever, amebic infections and kala-azar. References are given.

LESLIE, Evanston, Ill.

STUDIES ON THE PERIOD OF INCUBATION OF MUMPS. V. DE LAVERGNE, P. KISSEL and H. ACCOYER, Paris méd. **21**:477 (June 4) 1938.

During the course of an epidemic of mumps the authors obtained cerebral spinal fluid from children who had been in contact with patients, fifteen days after exposure. Certain specimens showed a slight increase in cells, and it was in the group of children from whom these specimens were obtained that mumps subsequently developed. In a later series specimens which contained increased numbers of cells were injected into rabbits. In half of the rabbits nerve lesions developed characteristic of infection with the virus of mumps. The authors conclude that invasion of the meninges precedes involvement of the parotid glands in the development of mumps. The mode of infection of the meninges and the subsequent distribution to other parts of the body are not clear at present.

LESLIE, Evanston, Ill.

SCARLET FEVER IN CHILE. B. VICUNA, Rev. chilena de pediat. **9**:844 (Oct.) 1938.

Vicuna has found that the Dick test is useful but not absolutely reliable. The susceptibility to scarlet fever thus determined in Chile is less than the statistics indicate for other countries. In 9.55 per cent of those who had had the disease the test was found positive. The scarlet fever anatoxin of the Bacteriological Institute when given in two doses is said to give good results. One dose alone does not affect the Dick test. The immunity conferred is less than that obtained with the antitoxin. There are no local or general reactions when intramuscular injections are given.

SCHLUTZ, Chicago.

MYOCARDIAL CHANGES IN DIPHTHERIA. L. OHEIM, Beitr. z. path. Anat. u. z. allg. Path. **100**:195, 1938.

A morphologic study of the myocardium in 50 fatal cases of diphtheria in which there were no complicating infections or other complicating conditions revealed the following successive changes: interstitial edema, myolysis, waxy degeneration, calcification, fatty degeneration, proliferation of fixed cells in the spaces arising from muscle cell degeneration, and leukocytic and lymphocytic infiltrations. Interstitial edema and initial myolysis appeared first on the second to the fourth day of the disease, while the other changes reached their height of intensity from the seventh to the thirteenth day. Reparation by connective tissue proliferation had commenced by the tenth day. The most severe lesions were encountered in the subendocardial and ring muscle layers of the myocardium, especially of that of the right ventricle. The significance of this distribution in respect to the efficacy of intravenous therapy is discussed.

LEBOWICH, Gloversville, N. Y. [ARCH. PATH.]

CEREBRAL COMPLICATIONS IN SCARLET FEVER. SUERMANN, Kinderärztl. Praxis **9**:460 (Nov.) 1938.

Suermann briefly reviews the literature on chorea, meningitis, abscess of the brain and encephalitis in patients with scarlet fever. In 1 of his own patients with scarlet fever encephalitis developed, with hyperkinetic symptoms, six days after onset of the fever. The spinal fluid showed 92 mg. of sugar per hundred milliliters. Pandy's test for globulin was positive (1 plus), and the number of white cells was increased over the normal.

HEYMANN, Cleveland.

DEMONSTRATION OF FREE DIPHTHERIA TOXIN IN PATIENTS' BLOOD. H. STEINMAURER, Med. Klin. **34**:463 (April 8) 1938.

Steinmaurer found unbound diphtheria toxin in the blood of 6 of 48 patients with diphtheria.

SIEMSEN, Chicago.

MENINGOCOCCIC SEPSIS RUNNING THE COURSE OF ERYTHEMA EXSUDATIVUM MULTIFORME WITH SUBSEQUENT MENINGITIS. H. E. BÜTTNER, Med. Klin. **34**:808 (June 17) 1938.

The title summarizes this report of a case well. Meningitis occurred thirty days after the onset of illness. Meningococci were demonstrated in the throat and pustular content and also in the spinal fluid obtained at the fourth lumbar puncture.

SIEMSEN, Chicago.

OBSERVATIONS ON PATIENTS WITH SCARLET FEVER DURING THE LAST FIVE YEARS. HÜGELSCHAFFER, Med. Klin. **34**:870 (July 1) 1938.

The diagnosis of scarlet fever is often difficult, but it is important to recognize the mild form of the disease, as this form may be responsible for an epidemic. Eosinophilia may aid in making the diagnosis. Recurrences are infrequent, but the fact that they occur indicates the importance of protecting convalescents from exposure to the infection.

SIEMSEN, Chicago.

SUPPURATIVE STREPTOCOCCIC LYMPHADENITIS FOLLOWING DIPHTHERIA IN BROTHERS. S. VON NIDA, Med. Klin. **34**:939 (July 15) 1938.

After pointing out the infrequency of streptococcic complications of diphtheria, von Nida describes 2 cases of streptococcic lymphadenitis with suppuration in brothers, who resembled each other in many respects, physically and mentally. He thinks the brothers had a similar "organ disposition" of the lymph glands.

SIEMSEN, Chicago.

NASAL DIPHTHERIA AND TONSILLECTOMY. J. BERBERICH, Pract. oto-rhino-laryng. **1**:311 (Sept.) 1938.

The author presents 5 cases in which tonsillectomy performed on a carrier of diphtheria resulted in disappearance of diphtheria bacilli in the nose. In view of this finding he suggests that there may be some special anatomic connection between the nose and the tonsils. PERSKY, Philadelphia. [ARCH. OTOLARYNG.]

Acute Infectious Diseases

CUTANEOUS MANIFESTATIONS OF TULAREMIA. J. M. HITCH and D. C. SMITH, Arch. Dermat. & Syph. **38**:859 (Dec.) 1938.

The primary ulcer of tularemia and the nodular lymphangitis seen in this disease are described from the clinical and from the microscopic standpoint.

The cases of tularemia in which there had been a generalized eruption are collected from the literature, and several new cases are added. The characteristic features of these eruptions are discussed and analyzed. The histologic structure of the lesions is given.

Experimental inoculation with tissue from a patient with the generalized eruption supports the contention that the eruption is toxic.

A generalized eruption may be the only suggestive sign in a case of tularemia.

FROM AUTHORS' SUMMARY.

NEWER CONCEPTS IN THE DIAGNOSIS AND TREATMENT OF JUVENILE RHEUMATISM. J. B. WOLFFE and V. A. DIGILIO, Arch. Pediat. **55**:424 (July) 1938.

The authors describe a chain of symptoms, varied and vague, which they feel may be a part of the rheumatic syndrome.

ORR, Buffalo.

LEFT UPPER ABDOMINAL PAIN ON EFFORT IN JUVENILE RHEUMATIC DISEASE—A NEW SYMPTOM OF THE LOW GRADE ACTIVE PHASE. V. A. DIGILIO, J. A. PESCATORE and H. E. GOLDBERG, Arch. Pediat. **55**:457 (Aug.) 1938.

Pain occurring in the abdomen, usually in the left upper quadrant, that is produced on walking or running is presumably associated with low grade active rheumatic disease. Exercise other than locomotion does not produce the pain. Six illustrative cases are presented.

ORR, Buffalo.

OUTBREAK OF BACILLARY DYSENTERY IN A CHILDREN'S CAMP. Health News **15**:141 (Aug. 22) 1938.

Of 500 children in a children's camp, 138 were attacked with abdominal cramps, nausea, vomiting, diarrhea and headache. They had temperatures from 101 to 102 F. Eight of these patients had Bacillus dysenteriae (Flexner) in their stools. Mucus and blood were found in the specimens in 10 per cent of the cases. The epidemic was due to fecal pollution of the water supply. Outbreaks of infection of this type in New York state are usually represented by gastroenteritis, but the presence of blood and mucus in the stools is exceptional.

AIKMAN, Rochester, N. Y.

CASES OF ROCKY MOUNTAIN SPOTTED FEVER ON LONG ISLAND. Health News **16**:6 (Jan. 9) 1939.

This disease occurred in 5 persons in Suffolk county during the summer of 1938. Three of the patients were children who had been bitten by ticks. Since the symptomatic picture may be suggestive of poliomyelitis, the warning is given that patients with such symptoms should be carefully searched for the presence of ticks.

AIKMAN, Rochester, N. Y.

AN EXPERIMENTAL STUDY OF THE TREATMENT OF PNEUMOCOCCAL TOXEMIA WITH A SPECIAL CARBON PREPARATION. G. E. ROCKWELL, J. Bact. **36**:272 (Sept.) 1938.

The intravenous injection of carbon is not new.

Although lobar pneumonia in man presents the clinical manifestations of a profound toxemia, it has not been possible to make a highly potent pneumococcic toxin. The toxin used in the present animal experiments was made by the method of Parker (anaerobic autolysis) or by that of Dick and Boor. The carbon used was animal charcoal dispersed in a saline-dextrose solution. The size, the charge on the surface and the volatile content of the particles was controlled. The preparations were standardized for their ability to absorb pneumococcic toxin. Mice which had been given lethal doses of the pneumococcic toxin could be saved by administering intravenously 1 mg. of carbon, even though the injection of carbon was delayed by as much as four hours after the injection of the toxin.

In 16 cases of pneumonia in man animal charcoal was injected intravenously in conjunction with the administration of antipneumococcus serum or of sulfanilamide. There was only one death. The number of cases of pneumonia in which the author tried this treatment is too small for statistical analysis. The good results suggest that charcoal may be a valuable adjunct in the therapy of pneumonia.

STOESSER, Minneapolis.

EXPERIMENTS ON ANTIRABIC IMMUNIZATION. A. HOYT, F. J. MOORE, M. K. GURLEY and D. WARNER, J. Bact. **36**:287 (Sept.) 1938.

The experiments of the authors are timely in view of the fact that several large cities in the country have experienced a number of cases of rabies among household pets. The investigators tested the serums of goats and rabbits which had been hyperimmunized with rabies fixed virus for neutralizing and protective properties. White mice were employed as the test animals. The virus was inoculated by the intracerebral route. Both goat and rabbit antiserums showed high neutralizing potency against fixed virus. In experiments on protection the rabbit serum proved greatly superior to the goat serum. Rabbit serum injected intraperitoneally before the inoculation of street virus brought about an extremely high percentage of survival, whereas almost all untreated control animals contracted rabies. Rabbit serum also demonstrated considerable protective effect even when administered as late as four days after the injection of street virus. Experiments on combined passive and active immunization against fixed virus showed that a single injection of antirabic rabbit serum given at the beginning of active immunization largely nullified the effect of twelve daily doses of vaccine. Mice receiving vaccine alone began to demonstrate active immunity immediately following five daily injections. Further vaccination produced a marked degree of immunity. Mice could not be protected against fixed virus if active immunization was begun after the inoculation of the virus. It was possible to protect mice when vaccination was started after the administration of street virus.

STOESSER, Minneapolis.

THE DIAGNOSIS OF RABIES. J. H. CONNELL, New Orleans M. & S. J. **91**:302 (Dec.) 1938.

During the past ten years there has been an increase in the incidence of rabies. The greatest incidence is in the most receptive host—dogs. In animals the diagnosis is based on (1) a history of contact and (2) an illness developing after an incubation of fourteen to twenty-one days. With active rabies, the least common form, the animal goes wild and terrorizes the neighborhood. With the more common form, the animal exhibits drowsiness and general apathy and appears quite innocuous. In either instance the saliva is infectious. The finding of Negri bodies in the brain makes the diagnosis positive.

Human rabies is always fatal. The diagnosis depends especially on a history of exposure. The period of incubation varies according to the distance of the injury from the cerebral tissue. It is from twenty-one days to six months, with cases being recorded in which it was two years. At the onset there are slight fever and nervous phenomena, which develop rapidly to marked apprehension, expressed in a fearful, staring expression. Disorientation follows, and extreme talkativeness develops. At the end there is inability to swallow, due to pharyngeal paralysis. Convulsions are not common. The temperatures vary from 101 to 103 F. The neck is rarely stiff, and the spinal fluid is negative as to pressure, cells and globulin. As in animals, the final diagnosis rests on the pathologic examination.

The most efficacious method of controlling the disease is to rid communities of stray animals.

BERKLEY, Los Angeles.

REPORTS OF A FEW CASES OF TETANUS TREATED WITH ANTI-TETANIC SERUM AND MAGNESIUM SULPHATE. P. PATERSON, Glasgow M. J. **130**:228 (Nov.) 1938.

Paterson used small doses of antitetanic serum (750 to 50,000, mostly under 20,000 units) and magnesium sulfate in 2.5 per cent solution, injected intramuscularly or subcutaneously. The results were excellent in 10 cases.

SNELLING, Toronto, Canada.

B. Pyocyaneus Infection Simulating Cholera and Acute Dysentery. H. Ghosh, J. Indian M. A. **7**:655 (Sept.) 1938.

Bacillus pyocyaneus (Pseudomonas aeruginosa) was found by culture of the stools of 5 patients having typical symptoms of cholera except for the stools, which were pink-colored and liquid owing to their content of blood. The absence of the vibrion of cholera and of all other pathogenic micro-organisms of the dysentery, typhoid or salmonella group was regarded as positive proof that these patients were infected with B. pyocyaneus. Even 0.25 cc. of a twenty-two hour broth culture killed an adult rabbit within eight to ten hours, thereby verifying the accentuated virulence of the organism.

Gonce, Madison, Wis.

Chemoprophylaxis of Malaria in Portuguese India. I. F. de Mello, South African M. J. **12**:710 (Oct. 8) 1938.

De Mello discusses the treatment of malaria considered as (1) an individual intercurrent disease and (2) a social, collective disease. The practical difficulties of treatment directed at the second object in rural areas often do not allow more than a mere drug prophylaxis. Because malaria varies from country to country it is not possible to have a universal standard treatment for all patients. For this reason de Mello outlines the general principles ruling the use of antimalarial products, in order to guide physicians in the establishment of local standard treatments.

Gonce, Madison, Wis.

Chronic Infectious Diseases

Immunologic Characteristics of Different Types of Tuberculin Reactors. M. Paretzky, Arch. Pediat. **55**:352 (June) 1938.

The immunologic characteristics of different types of reactors to tuberculin as observed in the clinics for persons with diseases of the chest of the Los Angeles County Health Department are reported. Paretzky considers it erroneous to include all persons with negative reactions in one large epidemiologic group. Tuberculin and clinical records if kept over a period of years reveal marked differences among them; accordingly, these persons should be divided into several different epidemiologic groups:

Group 1. Persistently negative reactors with efficient immunity. In this group are placed persons who have had repeated exposures to tuberculous infection over a period of years and who fail to react to old tuberculin even in high concentrations. These persons apparently possess very strong immunity, which not only protects them from the disease but enables them to remain free from tuberculoallergy.

Group 2. Formerly postitive reactors who have eventually lost their tuberculoallergy. Most of the patients listed under this classification were exposed to potent tuberculous infection and at one time reacted to old tuberculin but now have become desensitized to the extent of showing no reactions to large doses of tuberculin. This desensitization was in most instances rapid, and in many cases it was observed in spite of continuous exposure to infection. As a rule, these persons do not succumb to the disease. This group is considered to be endowed with immunity sufficiently potent not only to protect against the disease but to eradicate primary infections. In a considerable number tuberculoallergy reappeared.

Group 3. Negative reactors with low immunity. A number of negative reactors fail to react for a comparatively short period, and subsequently tuberculosis develops. In this group a variety of types of active tuberculosis develop. The prognosis for some of the patients is bad. A number of persons in this group

were compared with positive reactors. The difference was in favor of the positive reactors, substantiating the belief that in most cases a limited primary infection has a beneficial effect.

Group 4. Pseudonegative reactors. Persons in this group reacted only to higher doses of old tuberculin. Frequently they are classed as negative reactors since only weaker dilutions are employed in testing. It is the impression that this group consists of persons with fairly potent immunity. It is likely that their immunity is due to the implanted infection.

Group 5. Negative reactors later becoming positive reactors immune to tuberculosis. The majority of negative reactors remain so for a short time; eventually they become positive reactors, and they remain free from the disease. In the negative phase this group shows immunity sufficient to fight off the disease and to escape primary infection. Immunity is retained through the positive phase due to the added protection of immunity acquired from the implantation of the primary infection.

It is the author's impression, based on clinical observations, that exogenous infection plays by far the most important role in the spread of tuberculosis.

ORR, Buffalo.

ISOLATION OF THE BACILLUS TUBERCULOSIS FROM SPUTUM. A. SAENZ and J. T. PATERSON, Edinburgh M. J. **45**:818 (Nov.) 1938.

This communication comes from the Pasteur Institute, Paris, and was read at a meeting of the Edinburgh Tuberculosis Society. The authors conclude that for cultural purposes the sulfuric acid method of enrichment of the sputum is better than the use of antiformin because it is less toxic for the tubercle bacillus and more inhibitory for secondary organisms.

NEFF, Kansas City, Mo.

ARTIFICIAL PNEUMOTHORAX IN CHILDREN. P. F. FITZPATRICK, Irish J. M. Sc., November 1938, p. 727.

Fitzpatrick treated 2 patients for pulmonary tuberculosis by artificial pneumothorax. The results were excellent. He emphasizes that it is important to exercise care in the selection of cases.

SNELLING, Toronto, Canada.

TUBERCULOSIS IN AMERICAN SCHOOLS AND COLLEGES. E. R. LONG, Tubercle **19**: 241, 1938.

Studies continued over a decade indicate that the proportion of elementary and high school children giving positive reactions to the tuberculin test is steadily falling. In the less crowded communities the drop is more striking than in large, congested cities. The incidence of the positive result is generally significantly lower in rural communities than in urban areas, and differences within the same community are always found corresponding to differences in economic level. Important tuberculous disease is first encountered to an appreciable extent in high school students, in whom the combined incidence of latent and manifest disease varies from 1.5 to nearly 3 per cent, being higher in girls. Important disease demanding care occurs in from 0.5 to 1 per cent of these children. Active programs for the early detection and control of tuberculosis in schools now operate throughout the country. The basic principles of these programs are mass tuberculin testing, roentgen examination of the positive reactors and provision of suitable care for those found to have lesions. In the colleges about 6 students per thousand have tuberculosis of the adult type. A marked variation occurs geographically, students from the great central portion of the country having a relatively low incidence of the disease. Tuberculosis is recognized as the most serious disease of the college period, yet as insidious in onset, requiring routine mass measures for its detection. Most of the lesions now discovered are in the

minimal stage. Students of medicine and nursing are known to be subject to a special hazard. The danger for medical students seems greatest during the third and fourth, or clinical, years, suggesting that tuberculosis acquired in the medical school is usually exogenous. Most nurses who give a negative reaction to tuberculin on beginning training give a positive reaction during their course. The incidence of clinical tuberculosis is also proportionately high in nurses as compared with other professional or working groups at the same age, both during the period of training and in the first year after qualification.

FROM AUTHOR'S SUMMARY. [ARCH. PATH.]

OCULAR AND DENTAL MALFORMATIONS AND DISTURBANCES OF PERSONALITY IN TWO BROTHERS WITH HEREDITARY SYPHILIS. G. HEUYER and H. DUCHÈNE, Bull. Soc. de pédiat. de Paris **36**:100 (Feb.) 1938.

Two brothers, 14 and 15 years old, each had a congenital coloboma of the iris and abnormality of the teeth. They also had congenital syphilis.

BENJAMIN, Montreal, Canada.

LATE RESULTS IN NINE CHILDREN VACCINATED WITH BCG. M. GIOSEFFI, Lattante **9**:459 (Nov.) 1938.

A report in 1932 on 15 infants vaccinated with BCG showed that 7 had died between the second and ninth month but only 1 from tuberculosis. Late reports are given on 8 children who received BCG shortly after birth. These children are now between 3 and 10 years of age; 6 show negative reactions to both human and bovine tuberculin; 1, a positive reaction to human tuberculin, and 2 children, positive reactions to bovine tuberculin.

HIGGINS, Boston.

PSEUDOLEUKEMIC SPLENIC ANEMIA IN A SYPHILITIC INFANT. A. GUERRA and D. PICCARDO, Arch. de pediat. d. Uruguay **9**:494 (Aug.) 1938.

Guerra and Piccardo described a syphilitic patient 4 months of age who presented an interesting hematologic finding—severe anemia (hypochromic and oligocythemic), leukocytosis and increased myeloid reaction. Splenomegaly was marked. These changes were attributed to secondary erythroblastosis due to the syphilitic infection.

SCHLUTZ, Chicago.

WHEN TO TREAT CONGENITAL SYPHILIS. P. ARAYA, Rev. chilena de pediat. **9**:486 (May) 1938.

For purposes of treatment Araya classifies children with congenital syphilis into the following groups: (1) infants who give positive evidence of the disease clinically and serologically, who have to be treated at once; (2) children of syphilitic mothers who are clinically without sign of syphilis but who have a positive serologic test; (3) the doubtful group in whom clinical and serologic findings are negative but who have syphilitic mothers. The author suggests only close and very careful periodic examination, the examination to include diagnostic aids.

SCHLUTZ, Chicago.

PENTAVALENT ARSENIC IN THE TREATMENT OF SYPHILIS. A. DABANCENS and E. CASSORLA, Rev. chilena de pediat. **9**:825 (Oct.) 1938.

Pentarsil is used orally in tablets containing 0.125 Gm. of arsenic for syphilitic infants. So far 10 patients have been treated, with good results. When acetylated, the preparation yields acetarsone. It is given in doses of 4 tablets daily in seven series of ten days with four day intervals. Preparations of bismuth and mercury are also given at the intervals.

SCHLUTZ, Chicago.

INFLUENCE OF PURE VITAMIN PREPARATIONS ON COURSE OF TUBERCULOSIS IN GUINEA PIGS. R. STADLER and E. LARISCH, Jahrb. f. Kinderh. **146**:253 (April) 1936.

Diets rich in vitamins appear to exert a favorable influence on tuberculosis in guinea pigs. Vitamin C seems especially valuable, if one may judge from these experiments.

LANDAU, Hannibal, Mo.

INVOLUNTARY DEFECATION IN A NINE YEAR OLD GIRL WITH CONGENITAL SYPHILIS. V. MIKULOWSKI, Jahrb. f. Kinderh. **147**:23 (June) 1936.

An apparently healthy 9 years old girl was admitted to the hospital because of frequent involuntary defecation. She had syphilitic antecedents and was found to be syphilitic herself. No organic disturbance was demonstrated. A disturbance in the defecation reflex due to syphilis was considered to be the basis of her difficulty. Under antisyphilitic therapy she was relieved.

LANDAU, Hannibal, Mo.

HUMAN IMMUNITY AGAINST TUBERCULOSIS. H. VOGT, Monatschr. f. Kinderh. **76**:1 (Oct.) 1938.

This is a discussion as to whether tuberculosis is better combated by measures of immunization than by those of general hygiene. Vogt offers statistics showing that the primary lesion is appearing less frequently in early childhood and more frequently in later years. Infections occurring in the later years are milder than those occurring in the earlier years. Vogt believes that if one can ward off the early infection by general hygiene the child will overcome fairly easily an infection occurring later on. His tendency is to recommend measures of general hygiene for the protection of infants in preference to routine immunization with tuberculin.

GERSTLEY, Chicago.

Diseases of Blood, Heart and Blood Vessels and Spleen

PROTHROMBIN IN CHICKENS. F. SCHONHEYDER, Am. J. Physiol. **123**:349 (Aug.) 1938.

The hemorrhagic diathesis produced in chickens by a deficiency of vitamin K is due to a decrease of plasma prothrombin. It was demonstrated that the prothrombin in chicks is not identical with the midpiece of complement and that vitamin K deficiency does not affect the concentration of complement.

NOURSE, Cleveland.

CONGENITAL "ANEURYSMAL" DILATATION OF THE LEFT AURICLE. J. H. SEMANS and H. B. TAUSSIG, Bull. Johns Hopkins Hosp. **63**:404 (Dec.) 1938.

An enormous saccular dilatation of the left auricle in a 5 year old child is recorded. The condition is believed to have been due to a congenital abnormality either in the blood supply of the affected area or in the auricular myocardium. The thickening of the mitral valve and shortening of the chordae tendineae are believed to have been associated with the congenital malformation of the heart. The fact that the enormous saccular dilatation of the left auricle extended to the left and that it occurred in conjunction with incomplete dextrocardia offers strong evidence that both conditions represented congenital anomalies.

The literature concerning "aneurysmal" or "saccular" dilatation of the left auricle is reviewed. The case reported here is the only one in which the dilatation of the left auricle is believed to have been due to a congenital abnormality.

FROM THE AUTHORS' SUMMARY.

TUBERCULOUS ENDOCARDITIS OF THE PULMONARY VALVE. J. MARK, Bull. Johns Hopkins Hosp. **63**:415 (Dec.) 1938.

Miliary tuberculosis is described in which there was a distinct tuberculous polypoid vegetation limited to a leaflet of the pulmonary valve. The histologic appearance of the vegetation was characteristic of tuberculosis, and tubercle bacilli were present in great numbers. There was no evidence of involvement of the myocardium or endocardium by any other process.

FROM THE AUTHOR'S SUMMARY.

A STUDY OF BLOOD IODINE IN CHILDHOOD. G. J. FASHENA, J. Clin. Investigation **17**:179 (May) 1938.

Iodine was determined in the blood of 100 normal infants and children, ranging in age from that of the newly born to 13 years. For 79 subjects from 2 days to 13 years of age the blood iodine values varied from 3 to 12 micrograms per hundred cubic centimeters of whole blood, with an average of 6.6 micrograms; for 21 infants under 24 hours of age the values were significantly lower, ranging from 1 to 11 micrograms, with an average of 4.7 micrograms. Successive determinations on the blood of single infants revealed that the blood iodine increases with age within the first two to three weeks of life. No other consistent variations with age were observed. No significant differences between sexes were observed. No seasonal variation was found. The concentration of blood iodine was not increased in patients with fever of infectious origin. Determinations made on patients known to have thyroid disease yielded values which, although suggestively low in those with hypothyroidism and high in those with hyperthyroidism, frequently fell within the limits of the normal range for blood iodine. Such analyses, therefore, although useful in confirming a clinical impression, have little absolute significance.

GUEST, Cincinnati.

NUTRITIONAL ANAEMIA IN AN INDUSTRIAL DISTRICT. J. H. HUTCHISON, Arch. Dis. Childhood **13**:355 (Dec.) 1938.

A study of 300 infants provides evidence of the prevalence of iron deficiency anemia during the first year of life; 26 per cent of the total number of breast-fed infants and 35 per cent of the bottle-fed infants gave hemoglobin values at least 10 per cent below Mackay's normal values for their respective ages. These percentages become much greater if infants under the age of 6 months are excluded. The principal factors influencing the development of this type of anemia are discussed. They are: (1) undue prolongation of an exclusive milk diet; (2) low birth weight; (3) infections. The importance of prophylaxis is stressed, and methods of effecting this are discussed.

KELLY, Milwaukee.

RHEUMATIC ENDOCARDITIS AND PERICARDITIS. E. F. DOTT, Tr. Med.-Chir. Soc. Edinburgh, 1938, p. 181; in Edinburgh M. J., October 1938.

At a clinical meeting Dott showed a patient aged 11½ years who had been sick for a few weeks with rheumatic pain and signs of endocarditis. However, a heart murmur had been recognized at the age of 5 years, the rheumatism appearing first at 8½ years. Even in earlier childhood the heart was known to be enlarged. On admission to the hospital this year there were signs of acute rheumatism, pain in the cardiac area, a friction rub at the base, much cardiac enlargement and a blood sedimentation rate of 40 mm. In the ward the child showed at first distressed breathing with cyanosis, passive pleural effusion, fluid in the abdomen and an enlarged liver. Paracentesis gave much relief, a sedimentation rate of 25 and the disappearance of the friction rub.

Rheumatic carditis engrafted on a congenital lesion showed remarkable improvement following appropriate treatment, illustrating the recuperating power during childhood.

NEFF, Kansas City, Mo.

HAEMOLYTIC ANAEMIA IN A NEWBORN INFANT. T. B. SNELL, Proc. Roy. Soc. Med. **32**:96 (Dec.) 1938.

A girl aged 9 days was admitted to the hospital on account of anemia. On the second day of life she was noticed to have some jaundice and she became progressively paler. There was one other child of a seven months' pregnancy who died, aged 48 hours. The cause of death was unknown. On admission the patient was pale and feeble, and slightly jaundiced. The spleen was easily palpable below the costal region. No other abnormalities were elicited. A complete examination of the blood showed macrocytic anemia with a low red cell count and hemoglobin content but a high color index. The baby was accordingly given a transfusion with 50 cc. of the father's blood. Eleven more transfusions were given. The blood picture did not improve until after the tenth transfusion, which was incidentally the first one given of other than parents' blood. A complete blood count was made each day before each transfusion, and the counts are shown in tabular form in the report. No normoblasts were seen at the beginning, although good normoblastosis and also reticulocytosis appeared later. The results of further hematologic investigations accompany the report. WILLIAMSON, New Orleans.

FETAL HEART SOUNDS STUDIED BY THE PHONOCARDIOGRAPH. C. LIAN, V. GOLBEIN and G. MINOT, Bull. Soc. d'obst. et de gynéc. **27**:423 (June) 1938.

The authors used an apparatus by means of which the fetal heart sounds could be studied graphically and also recorded as sounds on phonograhpic disks. They found the fetal heart rate to vary between 140 and 160 per minute. They also discovered that contrary to general belief the fetal heart rhythm is not truly "pendular," as the French say, or "tic-toc," as we say, to indicate an equal interval between the sounds. The interval between the first and the second heart sound is 14/100 second and between the second and the first sound 16/100 to 19/100 second, so that in the fetus as in the adult there are a short and a long silence, relatively speaking, in the cardiac cycle. The first fetal heart sound has a duration of 6/100 second and the second sound one of 5/100 second. The vibrations of the second sound have a greater amplitude than those of the first sound, contrary to what one finds in adults. This finding, however, is not constant. A description of the sounds as amplified by a loud speaker is also given. Heard thus, the sound appears to be divided into three parts, owing to reduplication of the first sound.

GLASER, Rochester, N. Y.

STUDIES ON THE VOLUME OF THE CIRCULATING BLOOD IN CHILDREN WITH HEART DISEASE. U. GALLERANI, Riv. di clin. pediat. **36**:1057 (Dec.) 1938.

Using the "trypan red" method, Gallerani determined the volume of circulating blood in 16 children with acquired heart disease and in 2 children with congenital heart disease. One of the latter was cyanotic and the other not.

The number of cubic centimeters of plasma, cells and whole blood per kilogram of body weight is shown in the following tabulation.

	Cases	Volume of Plasma, Cc.	Volume of Cells, Cc.	Volume of Whole Blood, Cc.
Normal condition	61	47	30	77
Compensated heart disease	9	45	25	70
Decompensated heart disease	7	61	39	100
Congenital heart disease (cyanotic)	1	19	36	55
Congenital heart disease (not cyanotic)	1	42	28	70

In patients with decompensated heart disease the volume of plasma as well as of cells is increased. There is marked diminution of the blood volume of cyanotic patients with congenital malformation of the heart. HIGGINS, Boston.

GAUCHER'S DISEASE. A. ABALLI, F. PANICELLO and J. GISPERT, Bul. Soc. cubana de pediat. **10**:547 (Oct.) 1938.

These authors describe the first studies of Gaucher's disease in a Cuban child. The clinical impression was confirmed by the results of laboratory studies, including sternal and splenic puncture. There seemed to be a block or an obstruction of the reticuloendothelial system. Anatomic and histopathologic examinations showed characteristic lesions.

SCHLUTZ, Chicago.

FURTHER STUDIES ON WERLHOF'S MORBUS MACULOSUS; A HITHERTO UNKNOWN FAT-SOLUBLE T FACTOR WHICH CAUSES THROMBOCYTOSIS. E. SCHIFF and C. HIRSCHBERGER, Jahrb. f. Kinderh. **146**:293 (May) 1936.

Further experiments by Schiff and Hirschberger have led them to the conclusion that vitamin A-free sesame oil produces the same elevation of the platelet count as did the vitamin A concentrate in sesame oil used earlier. Children were given 8 to 10 drops daily. Olive oil did not contain the potent factor.

LANDAU, Hannibal, Mo.

A CLINICAL STUDY OF THE RETICULOCYTE COUNT IN BLOOD DISEASES OF CHILDREN. W. HEUBERGER, Jahrb. f. Kinderh. **146**:311 (May) 1936.

With goat's milk anemia blood regeneration as shown by the reticulocyte count begins much earlier and goes much higher than it does with cow's milk anemia. It is similar to that with pernicious anemia.

A 3 year old child with celiac disease under proper diet showed a great increase in reticulocytes, followed by a return to normal within a few days. A similar result was obtained with another child of 4. LANDAU, Hannibal, Mo.

CLINICAL STUDIES OF THE BEHAVIOR OF THE RETICULOCYTE COUNT. W. HEUBERGER, Jahrb. f. Kinderh. **147**:1 (June) 1936.

The reticulocyte counts of 2 infants after attacks of pneumonia showed a marked rise concomitant with improvement in the general condition, followed by a return to normal values shortly thereafter.

A 6 month old child with familial hemolytic icterus had a reticulocyte value 948 per cent of normal. This followed a sudden hemolytic crisis. In other children, following blood transfusions and iron and liver therapy, values of well over 100 per cent were found. Splenectomy was not carried out in any of these cases; consequently there were no reports on this.

A 50 year old man with pernicious anemia showed an extraordinary reticulocyte response following transfusion of 500 cc. of blood and liver therapy.

A 20 month old child who had lymphatic leukemia running the usual course had a reticulocyte count of but 12 per cent.

A 3½ year old child with sepsis and agranulocytosis had marked depression of all the blood cell elements and a reticulocyte count of 5 per cent. He died shortly after entrance to the hospital.

No reticulocyte increases above normal were found in eczematous infants.

LANDAU, Hannibal, Mo.

ARTERIAL HYPERTENSION IN INFANCY. S. BLAZSO and J. KRAMAR, Monatschr. f. Kinderh. **76**:51 (Oct.) 1938.

In a study of the blood pressures associated with acute illnesses Blazso and Kramar found arterial hypertension in some of their pneumonic patients as well as in those with toxic types of dysentery. After having ruled out organic lesions

in the nervous system, they came to the conclusion that the increased arterial pressure was due to circulating toxin. The spinal fluid of these patients caused hypertension when injected into animals.

GERSTLEY, Chicago.

ERYTHREMIC MYELOSIS. A. SAKAMOTO and K. TUKUNE, Monatschr. f. Kinderh. **76**:72 (Oct.) 1938.

A 19 month old boy, who was still receiving breast milk, presented a greatly distended abdomen, marked enlargement of the liver and spleen, and severe anemia. The leukocyte count varied up to 78,000, with many myelocytes. There were many nucleated red cells with a high percentage of reticulocytes. The autopsy showed a great amount of myeloid tissue in all the organs, especially in the kidneys, testes and dura.

GERSTLEY, Chicago.

Diseases of Nose, Throat and Ear

RETROPHARYNGEAL ABSCESS WITH FISTULIZATION INTO THE EXTERNAL AUDITORY CANAL. L. MERKLIN, Arch. Pediat. **55**:395 (July) 1938.

Two cases are reported.

ORR, Buffalo.

LARYNGITIS CHRONICA HYPERTROPHICA IN CHILDHOOD. H. ZISCHINSKY, Monatschr. f. Ohrenh. **72**:940 (Oct.) 1938.

Zischinsky describes laryngitis chronica hypertrophica as observed in 3 children. This form of laryngitis is not a specific chronic inflammation in the mucous membrane of the upper respiratory tract which heals by fibrosis. In 2 of these children the disease extended to the bronchi, a phenomenon not usually encountered in adults. The pathogenesis of the disease is not known. One of the children had measles associated with the development. The prognosis of laryngitis chronica hypertrophica seems to be worse for children than for adults.

LEDERER, Chicago. [ARCH. OTOLARYNG.]

TONSILLECTOMY IN THE PRESENCE OF ACUTE PERITONSILLAR ABSCESS. HISOMU MUKASA, Oto-rhino-laryng. **11**:829 (Sept.) 1938.

There is no unanimity of opinion as to the best time for tonsillectomy after the formation of a peritonsillar abscess. One group advocates the evacuation of the pus, to be followed later by tonsillectomy, when the inflammatory reaction has subsided in the tonsillar region. This group is known as interval operators. The second group, of whom the writer is one, believes that tonsillectomy should be done at the time the abscess is drained. They are called abscess tonsillectomists.

The interval operators point to the danger of spreading the infection when the operation is performed at the height of abscess formation. They say, secondly, that the patient is already weakened and that surgical procedure adds greatly to his discomfort.

Of 74 cases of peritonsillar abscess, Mukasa removed the tonsils in 63 at the time of evacuation of pus and in 13 performed drainage only. He also made comparative postoperative observations in 184 cases in which tonsillectomy was done after peritonsillar abscess.

Among the patients on whom tonsillectomy was done at the time of evacuation of the abscess, 69.2 per cent had no postoperative fever, and 30 per cent had varying degrees of fever on the second and the third postoperative day. Among those submitted to interval tonsillectomy, 67.2 per cent made an uneventful recovery, and 32 per cent had a rise of temperature on the second and the third postoperative day.

In the light of these figures the ill effects following abscess tonsillectomies appear no greater than those following interval tonsillectomies.

HARA, Los Angeles. [ARCH. OTOLARYNG.]

OCCURRENCE OF BLOOD IN AIR PASSAGES AFTER TONSILLECTOMY. TRULS LEEGAARD, Acta oto-laryng. **26**:467, 1938.

One hundred and nine patients, all over 14 and all operated on under local anesthesia, were examined. On 50 indirect laryngoscopic examination was made. The other 59 were studied after injections of a contrast material into the supratonsillar fossa had been made. The study showed that there was a considerable difference in the amount of blood and pharyngeal secretion appearing in the lower air passages according to whether the pharyngeal mucosa was anesthetized or not.

In 80 per cent of the patients (68 of 86) operated on after previous anesthetization of the mucous membrane larger or smaller quantities of blood and pharyngeal secretion were present in the lower air passages immediately after operation. In 15 of 23 patients operated on without previously painting the pharyngeal mucosa there were no postoperative traces of blood in larynx or trachea. In 7 cases single streaks of blood were noted and in 1 case much blood.

Of the 59 patients studied roentgenographically after injection of 1 to 2 cc. of iodized poppyseed oil into the tonsillar bed, 41 were operated on with and 18 without previous anesthetization of the mucous membrane. Contrast material could be demonstrated roentgenographically in the lungs of 31 of the 41 patients who had previous anesthetization and in only 5 of the 18 who had not, and in 4 of the latter there were only traces. The most common location of the contrast material was the middle lobe on the right side, corresponding to the straighter course of the right main bronchus. Leegaard feels that if the local tonsillectomy without previous anesthetization of the mucous membrane is performed in the recumbent position there is even less likelihood of blood entering the air passages.

GROVE, Milwaukee. [ARCH. OTOLARYNG.]

BACTERIOLOGIC AND CLINICAL STUDIES OF THE COMPLICATIONS OF SURGICALLY HANDLED ACUTE OTITIS MEDIA. EINO VAHERI, Acta oto-laryng., 1938, supp. 29, p. 1.

In an exhaustive study issued as a long supplement to the *Acta Oto-Laryngologica,* Vaheri discusses 200 cases of acute mastoiditis. Material for cultures was taken by syringe directly from the exposed mastoid cells. There were 83 further cases in which no organism could be obtained, and these were excluded from the study. The organisms found in the cases included were as follows:

	Cases	Percentage
Streptococcus haemolyticus	137	68.5
Streptococcus viridans	1	0.5
Pneumococcus type I	3	1.5
Pneumococcus type III	48	24.0
Pneumococcus type X (IV)	3	1.5
Staphylococcus albus	1	0.5
Staphylococcus aureus	2	1.0
Friedländer's bacillus	1	0.5
Streptococcus acidi lactici	1	0.5
Str. haemolyticus and Pneumococcus type I	1	0.5
Str. haemolyticus and Staph. aureus	1	0.5
Str. haemolyticus and Friedländer's bacillus	1	0.5

In no instance was the anhemolytic streptococcus encountered. Several of the colonies of streptococci which did not hemolyze blood immediately caused hemolysis on subsequent cultures. The statistics therefore indicate that in 92 per cent of all cases the mastoiditis was caused by either Str. haemolyticus or Pneumococcus type III. Vaheri has compared his findings with the statistics of Wirth and Hesse and found their statistics are similar to his.

Str. viridans is a rare organism in mastoiditis. Vaheri found it in only 1 case.

The staphylococcus is also relatively rare. Vaheri found it in 1.5 per cent of the cases. He found a mixed infection in the mastoidectomy wound in only 3 cases, or 1.5 per cent. Bacillus influenzae was never encountered in his material.

Clinically Vaheri divides his material into primary and secondary infections. He designates as primary infections otitis media and mastoiditis which develop without any acute concurrent condition, and 43 of the infections were primary. Of the secondary infections, 74 followed influenza, 36 an acute cold or sinal infection, 3 pneumonia, 3 sore throat, 2 peritonsillar abscess, 5 scarlet fever, 2 measles, 1 mumps, 2 an endonasal operation and 1 trauma. Of the infections due to Pneumococcus type III, 24, or 50 per cent, were secondary to influenza.

Vaheri is of the opinion that, while all the secondary otitic infections and a large part of the primary ones are exogenous, traveling up the tube, a part, at least, of the primary infections caused by Pneumococcus type X (IV) are endogenous.

The secondary otitic infections complicating influenza were caused by Str. haemolyticus in two thirds of the cases and by Pneumococcus type III in one third. In no case of influenzal otitis was B. influenzae found.

In otitic infections secondary to an acute cold or sinal infection, the bacteria found were about the same as in those secondary to influenza and occurred in about the same proportion.

Of the 3 infections secondary to pneumonia, 1 was caused by a Streptococcus and the other 2 by Pneumococcus type III.

In 30 of the 31 otitic infections complicating sore throat, a Streptococcus was found. The remaining infection was caused by Staph. aureus. All 5 of the infections complicating scarlet fever were due to Str. haemolyticus.

The otitis due to measles in his own cases and in those in the literature reviewed by him was caused by Streptococcus, Staphylococcus or Pneumococcus type III in about equal proportions.

CLINICAL OBSERVATIONS

The interval between the beginning of the primary disease and the appearance of otitis appears to be shorter with the streptococcic infections than with those due to Pneumococcus type III. The majority of the streptococcic infections begin with violent symptoms, but the initial symptoms of otitis due to Pneumococcus type III are much milder. Most of the otitic infections due to a Streptococcus begin with fever; those due to Pneumococcus type III begin without fever.

Most of Vaheri's patients were sent in from the provinces, and his histories indicate that otitis caused by a Streptococcus perforated the drum in an average of three and seven-tenths days after the aural symptoms were first noted, while in the infections due to Pneumococcus type III the period was ten days. Complications may ensue from otitis caused by Pneumococcus type III after the aural discharge has ceased.

According to the clinical course, he divided his material into an acute, a subacute and a latent type. Of the streptococcic infections, 7.3 per cent were acute, 26.3 per cent subacute and 3.4 per cent latent. Of the infections due to Pneumococcus type III, on the contrary, 14 per cent were acute, 15.3 per cent subacute and 33 per cent latent.

External perforations were more numerous in the infections due to Pneumococcus type III. Epidural complications were also more frequent in this type of otitis. Labyrinthitis, on the other hand, complicates the streptococcic infections more frequently than it does those due to Pneumococcus type III. The relative frequency of sinus thrombosis was about the same for both organisms. Tympanogenic meningitis is caused more frequently by the pneumococcus than by the streptococcus and appears later in the disease.

The mortality was higher in the infections due to Pneumococcus type III (10 per cent) than in those due to Streptococcus (4.4 per cent), and in the infections

due to Pneumococcus type III which have a lethal course the dangerous complications always develop late in the disease. A fatal complication may even occur after the discharge has ceased. GROVE, Milwaukee. [ARCH. OTOLARYNG.]

Diseases of Lungs, Pleura and Mediastinum

PNEUMONIA IN INFANCY AND CHILDHOOD. J. B. GILLESPIE, Illinois M. J. **74**:239 (Sept.) 1938.

This review of pneumonia in infancy and childhood is too comprehensive to be abstracted adequately. BARBOUR, Peoria, Ill.

NONSPECIFIC LUNG INFECTIONS IN CHILDHOOD. J. C. GITTINGS and R. C. FREDEEN, West Virginia M. J. **35**:16 (Jan.) 1939.

This is a splendid article, filling 18 pages and not condensable to the space available here. The authors define the conditions to be discussed; then, taking each in turn, they describe them, illustrating each with case histories and reproductions of roentgenograms. The study is based on an evaluation of the results observed in patients seen in the Children's Clinic of the Hospital of the Medical School of the University of Pennsylvania. It is a most practical study and one of great value to any one interested in conditions involving the chest.

SHAWKEY, Charleston, W. Va.

OBSERVATIONS ON THE TREATMENT OF EMPYEMA IN CHILDREN. H. L. WALLACE, Brit. M. J. **2**:560 (Sept. 10) 1938.

Wallace discusses in detail his experience covering fifteen years of hospital practice, which he summarizes as follows:

"A review is presented of several types of treatment employed in a series of cases of empyema in children occurring during a period of fifteen years. It is revealed that the success or failure of any form of treatment is governed to a large extent by the age of the child, the mortality reaching a very high level during infancy.

"The immediate effects of treatment by purely conservative measures are discussed, and these are contrasted with the results obtained by more radical procedures. It is apparent that, in those relatively few cases where the pus is very small in amount, cure can be effected without risk by conservative measures alone.

"In this series of cases the most successful method of treatment proved to be the operation of rib resection, performed immediately after localization of the empyema had been achieved by means of repeated aspiration. The mortality following this procedure was only 11.4 per cent., a figure which compares very favourably with that of other forms of treatment. Furthermore, the period of convalescence was found to be relatively short.

"The manner of drainage following rib resection did not appear to have any significant influence on the mortality, since a striking similarity was observed in the immediate effects of both closed suction and open drainage.

"The causal organism was proved to be the pneumococcus in 90 per cent of the cases in the series, the infection in the remainder being due either to the streptococcus or to the staphylococcus. The immediate results of treatment were not significantly influenced by the nature of the infecting organism."

ROYSTER, University, Va.

DYSPNOEA: A REVIEW. R. V. CHRISTIE, Quart. J. Med. **7**:421 (July) 1938.

The causes of dyspnea are discussed in this concise article. They are few and relatively simple; dyspnea originates in chemical and reflex disturbances. Christie

concludes that chemical dyspnea is of minor importance. He considers that reflex dyspnea is of great clinical importance and that it is associated with pulmonary congestion.

BRADFORD, Rochester, N. Y.

CAPILLARY BRONCHITIS: ITS TREATMENT BY VENOCLYSIS AND BLOOD TRANSFUSION. B. TASSOVATZ, Nourrisson **26**:288 (Sept.) 1938.

On the basis of his experience with capillary bronchitis in a patient 7 years of age, Tassovatz recommends treatment by withdrawal of 170 cc. of blood followed two hours later by transfusion of 120 cc. of blood.

HEYMANN, Cleveland.

CONGENITAL AIR CYSTS IN INFANTS. A. CARRAU, Arch. de pediat. d. Uruguay **9**:464 (Aug.) 1938.

Carrau described 2 cases of congenital air cysts of the lungs. The condition clinically simulated asthma. The diagnosis was confirmed by roentgenograms.

SCHLUTZ, Chicago.

CONGENITAL ABNORMALITIES OF THE LUNG AND ACQUIRED BRONCHIECTASIS. H. B. GOETTSCH, Nederl. tijdschr. v. geneesk. **82**:4516 (Sept. 17) 1938.

Congenital abnormalities of the lung have their proper symptomatic expressions, which can be totally altered by secondary infection. The resulting symptom complex often cannot be distinguished clinically or roentgenologically from that of an acquired disease. The congenital origin can be demonstrated if a roentgenogram is made before secondary infection supervenes. In the second case described, this condition was fulfilled, and the making of a faulty diagnosis was prevented.

VAN CREVELD, Amsterdam, Netherlands.

SYNDROME OF LÖFFLER. H. J. VIERSMA, Nederl. tijdschr. v. geneesk. **82**:5372 (Nov. 5) 1938.

Viersma describes 2 cases of Löffler's syndrome in adults: transient shadows in the lungs with hypereosinophilia and few clinical symptoms. It is presumed that there are different causes; Viersma mentions among others the possibility of infiltrates caused by larvae of Ascaris. One should guard against confusion of this condition with active tuberculosis.

VAN CREVELD, Amsterdam, Netherlands.

AGENESIS AND HYPOPLASIA OF THE LUNGS. P. FORMYNE, Nederl. tijdschr. v. geneesk. **82**:5482 (Nov. 12) 1938.

This is a description of a case of agenesis or very severe hypoplasia of the left lung, combined with numerous other congenital malformations, in a girl 19 years old. The clinical manifestations, the pathologic observations and the differential diagnosis are discussed.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

ANOREXIA. A. G. Dow, Nebraska M. J. **24**:96 (March) 1939.

Loss of appetite and consequent forced feeding, with an unreasonable amount of attention being focused on charts of weight, height and age, are important factors in anorexia. There are several reasons why a child will not eat: 1. He is sick. 2. He may not be hungry at the particular meal. 3. There may be a debilitating infection, as of tonsils and adenoids, or chronic colds, tuberculosis or pyelitis. 4. He may suffer from an allergy. 5. He may be constipated. 6. He may be teething. 7. His reluctance to eat may be a behavior problem. 8. He may

be fatigued. Attention to the vitamins is necessary. Presence or absence of anemia should be established. An iron tonic and cod liver oil may be beneficial; the latter should not be given before meals. If it is certain that no pathologic condition is present, it may be wise and safe to allow the sense of hunger to lead to an appetite.

HAMILTON, Omaha.

FOREIGN BODY IN THE UPPER ESOPHAGUS FOR FIVE MONTHS. M. C. MYERSON, New York State J. Med. **38**:885 (June 1) 1938.

A white girl aged 6 years complained of severe pain in the region of the upper part of the spine posteriorly. About five months previously she suffered from pain and discomfort in the throat. At that time she visited several dispensaries, without relief. Because of the localized symptoms, a roentgen study was made, and a jackstone was found lodged in the upper part of the esophagus. The tracheo-esophageal wall was markedly swollen, and it was necessary to insert a flexible tube into the trachea before an esophagoscopic examination could be made. The foreign body was removed successfully, and the child made a good recovery.

Pain and discomfort in the throat of a child should suggest the presence of a foreign body. The same is true of pain in the region of the spine.

AIKMAN, Rochester, N. Y.

SARCOMA OF INTESTINE IN CHILDREN. A. SIMPSON-SMITH, Brit. J. Surg. **26**:429, 1938.

This is a report of 2 cases of sarcoma of the intestine in a child, with a review of the literature on the subject. The author found accounts of 106 cases published during the past eighty years. The highest incidence was in the age group of 1 to 5 years and was progressively less in the groups from 5 to 15 years. The proportion of males to females was almost 3 to 1. Early diagnosis and treatment are difficult for three reasons: 1. Young children are affected usually and do not draw attention to early symptoms. 2. A small lump is sheltered in a large body cavity. 3. The growing sarcoma usually extends around the bowel wall, expanding rather than contracting the lumen, so that when obstruction occurs the growth is so large that it is too late for operative therapy. Only 24 per cent of the children with intestinal sarcoma have intussusception. In 90 per cent the symptoms have been noticed for only six months prior to admission to the hospital. Illness, pallor and wasting are commonly found. Abdominal pain and a palpable tumor (in 63 per cent of cases) are cardinal points in making the diagnosis. The author recommends a wide one stage resection, followed by a transfusion, with removal of mesenteric glands in the same careful way that the axillary glands are resected in a Halstead operation for carcinoma of the breast. From his review of the literature, the author finds the mortality to be 92 per cent.

KEITH, Toronto, Canada.

WINTER DIARRHEA IN INFANTS. S. GRAHAM, Practitioner **141**:733 (Dec.) 1938.

"It has been noted that since the beginning of the present century the morbidity and mortality from 'summer diarrhoea' have steadily decreased, so much so that at the present time the curve of infantile mortality shows its highest peak in winter instead of summer. Many of those infants dying in the winter months have diarrhoea, and it is with this aspect of the problem that the present communication proposes to deal.

"On consideration of etiological factors there are three groups into which all cases of diarrhoea in infants fall: (i) those due to dietetic causes, (ii) those due to infections in the bowel (enteral), and (iii) those occurring in the presence of infection outside the bowel (parenteral)."

The diagnosis, treatment and prevention of winter diarrhea are discussed.

GELSTON, San Francisco.

ACHALASIA. R. H. DOBBS, Proc. Roy. Soc. Med. **32**:92 (Dec.) 1938.

A boy of 6 years had been well until about a year before admission to the hospital. He then began to experience gradually increasing difficulty in eating. He vomited after every two or three mouthfuls at each meal but did not complain of pain. Occasionally, after two or three hours vomiting would occur, and a great deal of mucus and saliva would be brought up. The boy felt well but was always hungry and showed progressive loss of weight. Roentgen photographs of a swallow of barium sulfate showed moderate dilatation of the esophagus with gradual diminution in the size of the shadow, which ended bluntly at the level of the thoracic vertebra. None of the barium sulfate passed into the stomach. Under the fluoroscopic screen, persistaltic waves were seen passing down the esophagus, and a narrow trickle of the barium sulfate passed into the stomach. Esophagoscopic inspection, with the child under general anesthesia, revealed a moderately enlarged esophagus. The tube passed easily into the stomach, and bougies were passed up to the largest bronchial series. The child was made to swallow mercury bougies before each meal, and an improvement in the ability to swallow was immediately noticed. He at once commenced to gain in weight. The differential diagnosis is then discussed in the report.

WILLIAMSON, New Orleans.

STREPTOCOCCAL PERITONITIS WITH SEPTICEMIA. G. HERZFELD, Tr. Med.-Chir. Soc. Edinburgh, 1938, p. 190; in Edinburgh M. J., October 1938.

A little girl of 7 years with grave septicemia due to streptococcic peritonitis was treated nonsurgically, by conservative methods, with continuous intravenous dextrose saline drip and 40 cc. of prontosil soluble (disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonate, now known as neoprontosil), given intramuscularly, for seventy-two hours. A dramatic fall of temperature and a steady general improvement, followed by a brief second treatment with two injections of neoprontosil, stopped the disease so that at the end of three weeks the girl showed a complete return to health and activity.

NEFF, Kansas City, Mo.

DIAPHRAGMATIC HERNIA. E. VALLISNERI, Lattante **9**:416 (Oct.) 1938.

Two cases of congenital diaphragmatic hernia are reported. The first patient, an infant of 1 month, died of pressure on the mediastinum. The diagnosis at first was congenital malformation of the heart, but roentgenologic studies led to the correct diagnosis. The second patient, a child of 2½ years, had been coughing and vomiting for two months. The hernia was through the left costolumbar triangle. Surgical treatment of this infant was not yet deemed advisable.

HIGGINS, Boston.

PEPTIC ULCER PERFORATING INTO THE PANCREAS. J. BERTRAND and others, Arch. argent. de pediat. **8**:990 (Oct.) 1937.

This condition occurred in an 11 year old girl, who since the age of 2 had complained of recurrent attacks of abdominal pain and gastrointestinal upsets. The symptoms gradually progressed.

Observations in the hospital, confirmed by the results of roentgen and laboratory examinations, showed definite peptic ulcer.

Medical treatment was tried for a while, with little relief. Operative procedure was resorted to and a perforating peptic ulcer was found which penetrated into the adjacent pancreas, producing localized pancreatitis. The patient thereafter made a complete recovery.

SCHLUTZ, Chicago.

APPENDICITIS FROM OXYURIS INFESTATION. K. ANDRÄ, Arch. f. klin. Chir. **192:** 618 (Sept.) 1938.

At the Krankenhauses St. Georg, Leipzig, Germany, 150 (5.65 per cent) of 2,651 appendixes contained oxyurids. The findings in 96 of these typified Aschoff's oxyurid appendicitis (i. e., the presence of oxyurids with no histologic evidence of ulceration or scars). Many of the remaining appendixes presented larval forms deep in the mucosa or submucosa.

DAFFINEE, Boston.

Nervous Diseases

IMMUNOLOGICAL ASPECTS AND TREATMENT OF MENINGITIS. E. APPELBRUM, Arch. Pediat. **55:**400 (July) 1938.

The etiologic and immunologic aspects of meningococcic meningitis are discussed.

The case fatality of this form and other forms of meningitis as observed by the New York City Department of Health is reported.

The last time the department made an analysis of the cases of meningococcic meningitis in which it was responsible for the treatment, it found a mortality of 18.3 per cent in 302 cases covering a period of five years.

Of the 57 patients who died, 7 received only one injection of serum.

Best results are obtained by moderation in the use of serum. If there is no evidence of meningococcic septicemia, serum is indicated only for intraspinal injection.

Specific serum was used intraspinally in the treatment of influenzal meningitis, and recently prontosil (disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonate; now known as neoprontosil) and serum were combined and administered intraspinally. Of 18 patients, 2 recovered.

Pneumococcic meningitis was uniformly fatal until sulfanilamide was employed in therapy. Since that time in 32 cases 4 recoveries occurred. The recoveries concerned pneumococcus types XXXI, XX, IX, IV and XIII. Two cases, caused by types VI and III, respectively, are still under observation.

The case fatality of meningitis due to the hemolytic streptococcus has been reduced from more than 95 to about 20 per cent with the use of sulfanilamide. Twenty-six cases with 21 recoveries and 5 deaths are reported.

ORR, Buffalo.

BETA-HEMOLYTIC STREPTOCOCCUS MENINGITIS. A. T. MARTIN and S. L. ELLENBERG, Arch. Pediat. **55:**428 (July) 1938.

Two cases of recovery from streptococcic meningitis secondary to otitis media and mastoiditis are reported. The treatment consisted in removal of the focus of infection by mastoidectomy, daily spinal taps, administration of sulfanilamide, transfusion and supportive measures.

ORR, Buffalo.

FUTILITY AND DANGER OF INTRATHECAL MERCUROCHROME IN MENINGITIS. M. A. PERLSTEIN and A. LEVINSEN, Arch. Pediat. **55:**441 (July) 1938.

Mercurochrome is contraindicated in the treatment of meningitis, since it is too toxic to be introduced intrathecally in bactericidal strength.

ORR, Buffalo.

STREPTOCOCCIC MENINGITIS ORIGINATING IN THE MASTOID CURED BY ORAL AND INTRASPHENOID INJECTIONS OF SULFANILAMIDE. HALPHEN, RENE MARTIN and BIGNOTTI, Ann. d'oto-laryng., November 1938, p. 1033.

In an 11 year old child streptococcic meningitis (the organism was in the spinal fluid) developed from recurring mastoiditis. Sulfanilamide was given, and the dose

was based on the ratio of 0.15 Gm. per kilogram of body weight. It amounted to about 4 Gm., given by mouth at intervals of two or three hours, and 15 cc. of 0.85 per cent solution of sulfanilamide, injected into the subarachnoid space after preliminary withdrawal of an equal quantity of cerebrospinal fluid. The concentration of sulfanilamide in the cerebrospinal fluid was kept at about 4 mg. per hundred cubic centimeters of spinal fluid. The concentration in the blood was kept at about the same figure.

The authors refer to about 7 cases in which streptococcic meningitis has recently been reported in the French literature as cured. They point out that the ideal treatment is surgical drainage and prompt and adequate sulfanilamide therapy with oral and subarachnoid administration. This should result in a cure in the large majority of cases. The dosage is to be maintained for a sufficient length of time; else relapses tend to occur. The time may be from two to six weeks. This is best determined by the observations on the cerebrospinal fluid. Within four or five days organisms have generally disappeared from the spinal fluid. The concentration of sulfanilamide in the cerebrospinal fluid must be kept above 4 mg. per hundred cubic centimeters at the height of the disease. As a rule, improvement in symptoms occurs within a few days. If the symptoms clear, the dose may be carefully reduced.

The authors suggest that other measures should include supportive treatment, proper intake of fluid, a careful check on the blood cells and occasional transfusions.

McNALLY, Montreal, Canada. [ARCH. OTOLARYNG.]

TREATMENT OF ACUTE FORMS OF MENINGITIS WITH SULFANILAMIDE. L. TIXIER, Arch. de méd. d. enf. **41**:609 (Oct.) 1938.

Of a series of patients with cerebrospinal meningitis, due to invasions of either meningococcus B or unidentified strains of this organism, all those treated with sulfanilamide showed gratifying results. Another patient, in whom pneumococcus was concerned, likewise recovered. A reversal of former experience with this disease is generally noted. In discussing the various methods of administration Tixier recommends the buccal route for all patients except those whose illness is of extreme gravity. For these, intraspinal injections are employed. In either case large doses are used, and the administration is continued long enough to prevent relapse.

Sulfanilamide is also used as a prophylactic. It has proved of greatest value in immunizing contacts in institutions. The drug is exhibited also with extraordinary results in otitis media, in mastoiditis, in all contagious diseases and in severe anginas. Several case histories are reported in detail.

AMESSE, Denver.

EMBRYONAL SYMPATHETIC TUMOR IN A CHILD. R. DEBRÉ, J. LHERMITTE, P. UHRY, R. PARIS and ŒMICHEN, Bull. Soc. de pédiat. de Paris **36**:45 (Jan.) 1938.

A girl 8 years old was first observed at the age of 8 months, when she had a mass in the right side of the abdomen. Subsequently she had a mass in the left eyelid which looked like a palpebral hematoma, then one in the infraorbital region, whence it spontaneously disappeared after a month, then one in the internal surface of the right knee, on which a biopsy was made, and one subcutaneously on the back and another on the anterior aspect of the right thigh, which appeared to be retrogressing. Histologically, the tumor was made up of immature sympathetic cells with a fine collagen stroma. It was thought to be a sympathoblastoma, a type of tumor which usually develops in childhood, is less malignant than a sympathogonioma and more malignant than the more fully matured ganglioneuroma.

BENJAMIN, Montreal, Canada.

ACUTE LYMPHOCYTIC MENINGITIS VERY PROBABLY VERMINOUS. M. KAPLAN and J. CHAMPAULT, Bull. Soc. de pédiat. de Paris **36**:62 (Jan.) 1938.

Meningitis developed in a boy 13½ years old. There were 65 cells, mostly lymphocytes, per cubic millimeter in the spinal fluid. He was given santonin and passed some roundworms several days later. Following this, he recovered.

BENJAMIN, Montreal, Canada.

HEREDITY IN EPILEPSY. L. BABONNEIX, Gaz. d. hôp. **111**:1109 (Aug. 31) 1938.

This is an analysis of 344 cases which Babonneix has observed. Although 27 of the subjects had relatives subject to the same disease, it was not possible to exclude birth injuries and postnatal cranial injuries, and true heredity was probably much less frequent than would appear. Babonniex feels that the disease itself does not justify eugenic objections to the marriage of persons afflicted with it.

KADJI, Baltimore.

POLYRADICULONEURITIS WITH DISSOCIATION IN THE PROTEIN CONTENT AND CELLULAR CONTENT OF THE CEREBROSPINAL FLUID. H. ROGER and J. BOUDOURESQUES, Gaz. d. hôp. **111**:1157 (Sept. 10) 1938.

A survey of the literature on polyradiculoneuritis is completed with the authors' personal observations. They stress the involvement of the vegetative nervous system and the changes in the cerebrospinal fluid during the course of the disease.

Then they describe the differences in the clinical picture in children as compared with that in adults, namely, the presence of angina and rhinopharyngitis at the onset, the prominence of pain and the more rapid course.

They discuss the differential diagnosis from poliomyelitis and diphtheria and conclude that the condition described is an infectious disease due to a specific virus.

KADJI, Baltimore.

SOME CASES OF HEREDITARY CEREBELLAR ATAXIA. L. BABONNEIX and A. MENU, Gaz. d. hôp. **111**:1401 (Nov. 2) 1938.

Four persons in three generations were affected. The remaining 4 members of the family are too young for one to state whether or not they will escape the disease. Persons of both sexes were afflicted. The onset was progressively earlier in subsequent generations. The absence of scoliosis and of deformities of the feet is emphasized.

KADJI, Baltimore.

ADIE'S SYNDROME IN A CHILD. L. BABONNEIX, H. GRENET and J. SIGWALD, Rev. neurol. **67**:622, 1937.

A child had paralytic mydriasis and paresis of accommodation of the left pupil. The eyegrounds were of the hypermetropic type. The right eye was normal. The nasopalpebral and cochleopalpebral reflexes were markedly diminished. The achilles and medioplantar reflexes were absent on both sides. The knee jerks, the reflexes of the upper extremities and the various cutaneous reflexes were all normal. All modes of sensation were normal. There was no Romberg sign. The Wassermann reaction of the blood was negative. Examination of the spinal fluid showed no evidence of syphilis. The father was said to have seizures and had been treated with phenobarbital. The mother and a sibling seemed to be in good health. The patient was observed for two years; no change in the condition was noted.

LIBER, New York. [ARCH. NEUROL. & PSYCHIAT.]

JUVENILE AMAUROTIC IDIOCY. G. MARINESCO, Rev. neurol. **69**:449 (May) 1938.

Marinesco discusses a recent study of Dide and van Bogaert dealing with the Dollinger-Bielschowsky type of delayed amaurotic idiocy. He stresses the role of ferments and physicochemical changes in the development of the lesions. He suggests that the lipidosis which gives a senile appearance to the nerve cells is not a process of progressive intoxication but a physicochemical change occurring in the serum of a young body.

DAFFINEE, Boston.

MULTIPLE SCLEROSIS IN CHILDREN. L. RIMBAUD, RISER and GÉRAUD, Rev. neurol. **69**:477 (May) 1938.

Three children aged 7, 9 and 12 years presented typical symptoms of multiple sclerosis. In all the sclerosis was a sequela of a grippal infection. The clinical picture developed rapidly, with difficulties in speech and cerebellar signs. In 2 children mental changes developed, with optic neuritis. In one the condition progressed to convulsions and death; the other recovered. The third child has been lost to observation. There were no sensory changes, no atrophic paralyses, no vertigo. One child showed the typical changes in the spinal fluid. In the fatal case autopsy was not performed.

DAFFINEE, Boston.

TREATMENT OF CHOREA WITH MAGNESIUM SULFATE. A. M. ABRIL, Arch. de med. inf. **6**:222 (June) 1937.

Abril reports very satisfactory results from injecting 20 per cent magnesium sulfate intramuscularly every other day in the treatment of chorea in children. Improvement was noted after the fourth or the fifth injection.

SCHLUTZ, Chicago.

MEDULLOBLASTOMA ASSOCIATED WITH THE ADIPOSOGENITAL SYNDROME: CLINICAL NOTE. M. FUENTES, Arch. de neurol. y psiquiat. de Mexico **1**:296, 1938.

An 11 year old boy six months after a fall on the head experienced severe headaches, failing vision, vomiting, polyphagia, polydipsia and increase in weight. In the following two years the size of the head increased notably; blindness became complete; headache, vomiting and dizziness continued, and somnolence, disequilibrium and mental detardation, with incoherent speech and a tendency to confabulation, developed. Physcial examination revealed a typical adiposogenital syndrome with testicular involution. Neurologic examination showed no definite localizing signs. Lumbar puncture revealed marked increase in pressure. A ventriculogram showed enormous dilatation of the lateral ventricles. Exploration, with a right frontoparietal approach, was performed, but the tumor was not located. Death occurred in a few days. Autopsy revealed a large tumor of the cerebellum, occupying the roof of the fourth ventricle, extending through the aqueduct and spreading to the internal walls of both lateral ventricles, the floor of the third ventricle and the pia over the vermis and cerebellar lobules. The tumor was diagnosed as a medulloblastoma or isomorphous glioblastoma. The author believes that the adiposogenital syndrome was produced by the tumor, although the hypophysis was normal.

MEEHAN, Princeton, N. J. [ARCH. NEUROL. & PSYCHIAT.]

DIAGNOSTIC DIFFERENTIATION OF EPILEPSY FROM PYKNOLEPSY AND SALAAM CONVULSIONS IN CHILDREN. U. MOELLER, Jahrb. f. Kinderh. **146**:240 (April) 1936.

Attempts were made to differentiate the various types of epileptiform convulsions by using different methods of bringing them about, such as injections of pituitary substance, hyperventilation and alkalinization. It is felt that this

method of approach has definite possibilities. In the differentiation of pyknolepsy (often known as petit mal) hyperventilation was judged to be 93 per cent accurate.

In the differentiation of true or advanced epilepsy alkalinization, in the author's opinion, is valuable, and injection in that of the salaam type (a classic description of a certain type of convulsion) of pituitary gland is also considered of value. The results with the latter two methods are not as conclusive as those with hyperventilation in the case of pyknolepsy. LANDAU, Hannibal, Mo.

REPORT ON CEREBRAL ABSCESS OBSERVED AT THE EAR CLINIC IN AGRAM. A. SERCER, Monatschr. f. Ohrenh. **72**:946 (Oct.) 1938.

Sercer reports 34 cases of otogenic cerebral abscess observed at the clinic in Agram during the past sixteen years. On the basis of those cases the well known facts about the pathologic picture and clinical course of cerebral abscess are repeated and the literature quoted rather superficially. As far as the treatment is concerned, it is mentioned quite hypothetically that injection of drugs (rivanol) into the carotid artery may increase the local reaction of the brain tissue around the abscess and hinder the propagation of encephalitis.

LEDERER, Chicago. [ARCH. OTOLARYNG.]

MASS AND SURFACE DEVELOPMENT OF THE FETAL BRAIN. H. H. MEYER, Virchows Arch. f. path. Anat. **300**:202, 1937.

The brains of 180 fetuses between the fifth and tenth month of pregnancy were studied as to changes in weight in reference to fetal length and as to the time and appearance and development of the more important sulci and convolutions. The time of appearance of the main sulci and the peculiarities of their developments are summarized in a series of tables, the material being grouped according to weeks of duration of pregnancy as determined by fetal length. In their earliest development the sulci are bilaterally symmetric, but the symmetry is disturbed by the formation of anastomoses and other developmental changes. There is no direct correlation between the general development of the body and the development of the brain. The sulci of the brains of female fetuses revealed a greater degree of variation as the result of anastomosis between sulci than did brains of male fetuses. O. T. SCHULTZ, Chicago. [ARCH. PATH.]

TUMORS OF THE BRAIN. O. GAGEL, Ztschr. f. d. ges. Neurol. u. Psychiat. **161**:69 (March) 1938.

Gagel found that 4.6 per cent of all (560) patients admitted to an active neurologic service had tumor of the brain. In 198 of these cases the tumor was in one of the cerebral hemispheres; in 150, at the base of the brain; in 118, in the spinal cord, and in 56, in the cerebellum. In addition, there were 34 cases of tumor of the cerebellopontile angle and 2 of tumor of the peripheral nerves. The large number of cases of tumor at the base of the brain is noteworthy; in 54 of these the growth was in the chiasmal region; in 19, in the basal ganglions; in 9, in the thalamus; in 15, in the third ventricle; in 22, in the region of the corpora quadrigemina; in 17, in the fourth ventricle, and in 14, in the pons and medulla. In 305 cases the tumor was of neuroepithelial origin. In the other group of 255 cases there were 76 of meningioma, 7 of neurofibroma, 31 of metastatic tumor, 29 of sarcoma or carcinoma, 22 of hypophysial adenoma, 17 of craniopharyngeoma, 10 of hemangioblastoma, 7 of hemangioma, 10 of cysticercus cyst, 8 of chondroma, 6 of epidermoid, 2 of dermoid cyst, 6 of lipoma, 6 of arachnoid sarcoma, 6 of cysts, 4 of tuberculoma, 2 of teratoma, 2 of osteoma, 2 of gumma, 1 of chordoma and 1 of melanoma.

Gagel limited his study to cases of tumor of neuroepithelial origin. There were 2 of neuroepithelioma; in both the tumor arose from the floor of the third

ventricle. There were 25 of medulloblastoma (13 of the patients were males and 12 females); in 19 the lesion was in the vermis, and in 2, in the cord; in 1 case each, the third ventricle, pons and temporal lobe were involved, and in 1, the retina and optic nerve. There were 9 cases of gangliocytoma, a tumor composed predominantly of ganglion cells. In these cases the patients were all young persons: 6 males and 3 females. The tumor occurred especially in the brain stem.

In 16 cases the tumor was a polar spongioblastoma (9 of the patients were females and 7 males). In most of these cases the tumor occurred in the later half of life. In most instances it was located in the brain stem and was inoperable. There were 4 cases of astroblastoma in the white matter of the cerebral hemispheres and in the corpus callosum. The characteristic attachment of the main process to the blood vessels was readily seen. There was little fiber formation. Cases of astrocytoma were more numerous (32 of the patients were males, harboring 58 growths, and 26 females). In most of these cases the patients were young persons, owing to the high incidence of cerebellar astrocytoma. In 12 cases the lesions were in the cerebellum; in 22, in the cerebral hemispheres; in 5, in the third ventricle; in 4, in the fourth ventricle; in 4, in the pons; in 4, in the cord; in 3, in the basal ganglions; in 2, in the thalamus, and in 2, in the corpus callosum. In most of the instances of hemispheral tumor the frontal lobe was the site.

Glioblastoma multiforme (or, more properly, malignant glioblastoma) is the commonest gliogenous tumor. There were 84 cases of it in the series (55 of the patients were men and 29 women). The tumor was seen especially in the cerebral hemispheres. In no case was it observed in the cerebellum. It was encountered most frequently about the fortieth year. Three types can be clearly differentiated: the microcellular glioblastoma, containing the small cells resembling medulloblasts; the fusiform glioblastoma, with long cells resembling polar spongioblasts, and the glioblastoma multiforme, containing polymorphonuclear giant cells and characterized by intense polymorphism. Mitoses were most numerous in the small cell glioblastoma. This microcellular glioblastoma may extend into the leptomeningeal tissues.

There were 5 cases of oligodendroglioma—in 3 it was in the cerebral hemisphere, and in 2, in the spinal cord. It was a slow-growing tumor and usually contained relatively large deposits of calcium. It was subcortical and not sharply delimited from the normal brain tissue. Thirty cases of ependymoma were observed (21 of the patients were men, and 9 were women—their ages ranged from 20 to 40). The most common site was the region of the fourth ventricle (7 cases) and the spinal cord (7 cases). In 5 cases each the region of the third ventricle and the aqueduct were involved; in 4 cases the lateral ventricle was the site, and in 1 case each the cerebellum and the cortex were implicated. Six cases of papilloma of the choroid plexus were seen—in 4 cases the tumor was in the fourth ventricle; in 1, in the foramens of Monro, and in 1, in the occipital lobe. Calcification and implants from the spinal fluid were seen. There were 11 cases of pinealoma, with the usual predominance (9 cases) in males.

SAVITSKY, New York. [ARCH. NEUROL. & PSYCHIAT.]

TUMOR OF THE BRAIN IN YOUNG PERSONS. K. J. ZÜLCH, Ztschr. f. d. ges. Neurol. u. Psychiat. **161**:183 (March) 1938.

Zülch studied the problem of tumor of the brain in 121 patients between 1 and 20 years of age. The following significant facts were noted: The temporoparieto-occipital region of the cerebrum was most often involved, especially by ependymoma; the ganglion cell tumor was seen in large numbers. Meningioma was rare, and there was no instance of tumor of the angle; tumor of the cerebellum was most frequent; craniopharyngioma and pinealoma were often encountered; in 4 of the 5 cases of astrocytoma of the aqueduct of Sylvius the neoplasm occurred in young persons.

SAVITSKY, New York. [ARCH. NEUROL. & PSYCHIAT.]

GENETIC STUDIES ON TUMOR OF THE BRAIN. K. E. PASS, Ztschr. f. d. ges. Neurol. u. Psychiat. **161**:204 (March) 1938.

Pass studied 30 families of patients with tumor of the brain. Only parents, siblings and children were investigated, making 222 persons in three generations. Of these, 76 had died; 109 of 146 of the living (76 per cent) were studied. In only 1 family was there a familial incidence of tumor of the brain: One patient with glioma in the frontal lobe had a half-sister with a similar tumor. Twenty-six of the 222 relatives of patients with verified tumor of the brain had tumors in other parts of the body (12 of which were benign and 14 malignant). Recklinghausen's disease was found in another member of the family in 3 instances. Pass concludes that there is no evidence for a genetic basis of tumor of the brain, that there is a relation between tumor of the brain and Recklinghausen's disease, that there are grounds for the existence of an anlage to tumor formation in general and that there is no demonstrable connection between the incidence of tumor of the brain and that of other nervous and mental diseases.

SAVITSKY, New York. [ARCH. NEUROL. & PSYCHIAT.]

A NEW METHOD IN THE TREATMENT OF TRIGEMINAL NEURALGIA. O. RIED, Acta med. Scandinav. **96**:105, 1938.

Ried obtained favorable results by injecting locally sodium chloride and sodium sulfate solutions irradiated with ultraviolet rays. Within a few minutes after injection pain ceased, and the effect lasted for several days.

KAJDI, Baltimore.

HEREDITY AND EPILEPSY: V. THE PROBLEM OF EPILEPTOID PSYCHOPATHY. K. CONRAD, Ztschr. f. d. ges. Neurol. u. Psychiat. **162**:505 (May) 1938.

The incidence and the nature of disorders of character and personality were studied in all children aged over 20 of 553 epileptic persons. There were over ten times as many abnormal persons in the idiopathic (77:911) as in the symptomatic (2:275) group. The explosive and emotional types predominated, constituting about 40 per cent of those who showed psychopathic reactions in the idiopathic group. In Stumpf's study of the siblings of recidivists there were only 20 per cent of this type, and in Riedl's study of the children of psychopathic persons there was only 1 per cent. Pedantry, bigotry, fanaticism, seclusiveness and religiosity were not prominent. Thirteen per cent of the children over 18 of persons with idiopathic epilepsy came into contact with the law, as compared with a normal incidence of 5 per cent. The incidence of delinquency in the idiopathic group was about four times that of the symptomatic group. Most of the crimes resulted from quarrels with persons in the immediate environment. Stealing, forgery and embezzlement were less frequent; begging was common. Much of the criminality evidently arose from the marked affective lability of epileptic persons. The suicide rate was 5.7 per cent in the idiopathic group. The control average given by Conrad was 3.2 per cent. The difference is not significant. The suicide rate for the children of persons with idiopathic epilepsy may be explained by the relatively younger age of this group as compared with the controls. Suicidal attempts in this group were usually impulsive and unaccompanied by depression and were not in reaction to an adequate situation.

The author suggests that the term "epileptoid psychopathic" be avoided. He prefers to use the descriptive terms "explosive" and "emotionally labile." The abnormal frequency of the explosive and emotionally labile psychopathic types in a particular family has value in the diagnosis of hereditary epilepsy.

SAVITSKY, New York. [ARCH. NEUROL. & PSYCHIAT.]

Diseases of the Ductless Glands; Endocrinology

End-Results of Irradiation of the Thymus Gland in Twenty-Four Normal Infants and Children. C. G. Kerley, Am. J. Roentgenol. **40**:416 (Sept.) 1938.

In 24 cases an attempt was made to determine the therapeutic results and absence of harm on mental or physical development of irradiation of an enlarged thymus gland.

The diagnosis was made by a roentgenogram of the chest and a history of sudden alarming attacks of dyspnea with cyanosis in an infant who otherwise was healthy.

In 21 cases the age range at the time of treatment was less than 1 year. The weight and height of all the children except 2 were above the standards.

The author concludes that if the child is normal irradiation of the thymus produces no retardation of physical growth or of mental development.

Squire, Chicago.

Certain Therapeutic Effects of Whole Suprarenal Gland by Mouth. O. E. Barbour, Arch. Pediat. **55**:661 (Nov.) 1938.

Over 380 patients are included in this study. Desiccated whole adrenal gland was administered to infants or children of the allergic or vagotonic type. The optimal dose seemed to be 1 grain (0.064 Gm.). If the conditions treated were acute, the substance was administered at two or three hour intervals.

One hundred and forty children with bronchial asthma were treated, and relief was obtained in 74 per cent. The adrenal gland seemed to assist in the cure of 32 of these children.

Forty-four patients with spasmodic croup were treated, and relief was obtained in 90 per cent.

Eighty infants suffered from pylorospasm; vomiting was relieved in 90 per cent. In those in whom improvement did not occur within one or two days, adrenal gland was augmented with iodine or thyroid gland, a procedure which usually produced the desired results.

Eighty patients with eczema were treated, and adrenal gland was effective alone or when administered with iodine or thyroid gland in relieving 80 per cent. Improvement was prompt, usually occurring within one or two days. When the optimal dosage was obtained and maintained, the skin remained free from the rash in 80 per cent of the patients. Food allergy presented no great problem when endocrine therapy was employed.

In treating 40 patients with hypothyroidism, adrenal substance proved most valuable when used in conjunction with thyroid substance. More adequate amounts of thyroid could be administered when adrenal material was administered than when thyroid was given alone.

For purposes of comparison and as partial controls, treatments other than that with desiccated adrenal gland were given alternately or concomitantly at intervals through the course of this study. Drugs which simulated the therapeutic action of adrenal gland were ephedrine and neosynephrin.

Iodine and atropine reacted to the adrenal therapy much as did thyroid gland. They appeared to inhibit the untoward reactions and at the same time to enhance the effectiveness of the therapy. In some patients untoward reactions occurred while adrenal gland was being administered, such as abdominal pain, vomiting and constipation.

Orr, Buffalo.

Oral Administration of Hormonal Proteins. H. Wilson, T. S. Sappington and W. T. Salter, Endocrinology **23**:535 (Nov.) 1938.

Insulin is generally said to be "inactive when taken by mouth." But it is shown here that even after rather drastic hydrolysis by pepsin the "destroyed" insulin can be recovered in part by the addition of alkali.

This finding suggests that under appropriate circumstances the oral administration of insulin may be effective.

In fact, the oral administration of insulin preparations in mice has consistently and reproducibly produced hypoglycemic coma or convulsions within two hours. The oral dose observed for undigested insulin hydrochloride was about ninety times its subcutaneous dose. The oral dose observed for digested insulin was about forty-five times its subcutaneous dose. Iron salts increased the effectiveness of insulin and of digests of insulin when administered orally.

These observations suggest qualitative similarities between thyroglobulin and insulin with respect to the action of proteolytic enzymes. They suggest, further, that hormonal proteins can be used orally under suitable conditions.

JACOBSEN, Buffalo.

CERTAIN IODINE-REDUCING SUBSTANCES OF THYMUS EXTRACT. L. G. ROWNTREE, A. STEINBERG, N. H. EINHORN and N. K. SCHAFFER, Endocrinology **23**:584 (Nov.) 1938.

Glutathione, ascorbic acid and cysteine in the dosage reported here are all capable of accelerating the rate of development of the offspring of treated rats, whereas glutathione, in addition, is capable of accelerating growth. The biologic effects of these iodine-reducing substances simulate those of thymus extract in many respects but in a number of other respects fall short of the effects of thymus extract.

JACOBSEN, Buffalo.

JUVENILE ADIPOSOGENITAL DYSTROPHY, NEUROLOGIC AND PSYCHOPATHOLOGIC ASPECTS, RESULTS OF ORGANOTHERAPY AND PSYCHOTHERAPY. B. MITTELMANN, Endocrinology **23**:637 (Nov.) 1938.

This is a study of 16 boys with adiposogenital dystrophy.

The neurologic disturbances may be limited to muscular hypotonia or may include clumsy motility, tendency to postural reflexes which deviate from the adult norm, intention tremor or inequality of the associated arm movements, spasmodic torticollis and nystagmus. Psychopathologic manifestations referable to the syndrome may be absent.

When present, the chief psychopathologic manifestations are depression, oversubmissive, overdependent and/or overaggressive, hostile behavior disturbance. The psychopathologic aspects proper of the adiposogenital dystrophy are usually interwoven with psychopathologic characters traceable to problems of development and of the family environment (transference neuroses) and not directly connected with the syndrome. The best management of the condition consists in correction of the endocrine disturbance together with adequate psychotherapy at any age when the patient comes under observation. The psychotherapeutic results are satisfactory in the majority of the cases.

JACOBSEN, Buffalo.

INDUCTION OF PREMATURE PUBERTY WITH ANDROGENIC SUBSTANCE. R. H. KUNSTADTER, Endocrinology **23**:661 (Nov.) 1938.

In 2 sexually retarded boys, aged 11½ years and 10⅔ years, respectively, premature puberty was induced by intramuscular injections of androgenic substance (testosterone propionate). In the 11½ year old boy, in addition to premature puberty, abnormal genital hypertrophy resulted. At the onset of treatment both boys presented small genitalia, which were not considered dystrophic. In view of the results obtained in these patients, the danger of administering a potent androgenic substance to young persons should be realized.

JACOBSEN, Buffalo.

CLINICAL USE OF A NEW ESTROGEN. R. R. GREENE and E. M. DORR, Endocrinology **24**:577 (April) 1939.

Success in treatment with the estrogenic substances now in clinical use necessitates intramuscular injections two to four times weekly in the majority of cases. Oral therapy is of value in some instances, but the cost per effective unit of the present available forms makes their use except in a very few patients financially prohibitive.

Estradiol dipropionate, because of its prolonged physiologic effect as compared with other commonly used estrogens (shown by animal experimentation), was used clinically in a variety of cases, including 9 of infantile vaginitis. The findings seem to justify the conclusion that it is possible with this preparation to obtain good results with smaller and less frequent injections. JACOBSEN, Buffalo.

THE THYMUS STUDIES OF SOME CHANGES IN THE GONADS AND PITUITARY FOLLOWING ITS DESTRUCTION BY ROENTGEN IRRADIATION. H. SHAY, J. GERSHON-COHEN, S. S. FELS, D. R. MERANZE and T. MERANZE, J. A. M. A. **112**:290 (Jan. 28) 1939.

Experiments on the rat in which the thymus was completely or almost completely destroyed by irradiation revealed that testicular development was arrested but resumed after one hundred and fifty days until fertility returned. Coincidentally, the pituitary was hypoplastic. If conclusions can be carried over to man, it seems that the usual therapy directed to the thymus should be harmless.

HEERSMA, Kalamazoo, Mich.

JUVENILE DIABETES MELLITUS. H. M. FEINBLATT, J. Lab. & Clin. Med. **24**:337 (Jan.) 1939.

In a series of cases of juvenile diabetes, the best results were obtained with protamine insulin. McMURRAY, Galveston, Texas.

TUMORS OF THE ADRENAL GLAND IN EARLY CHILDHOOD, WITH A REPORT OF TWO CASES. A. R. MORGAN, New Orleans M. & S. J. **91**:345 (Jan.) 1939.

Two cases of adrenal tumor are presented. The first was that of a boy of 3 years, operated on in March 1937. The tumor mass was the size of a grapefruit and involved the entire right kidney. Microscopic sections showed embryonal myosarcoma. When seen recently, the boy weighed 40 pounds (18 Kg.) and seemed normal.

The second case was that of a boy 20 months old. He was operated on in March 1937, and a roughly oblong nodular tumor, measuring 4½ by 3 inches (11.5 by 7.5 cm.), was removed. The color varied from dark brown to translucent yellowish. There were several cysts in the mass and several hemorrhagic areas. The tumor had invaded the upper third of the renal substance. Microscopic sections showed adrenal sarcoma. The child is alive and well, with no signs of metastasis at the date of writing. BERKLEY, Los Angeles.

A CASE OF THORACIC DEFORMITY. HEUYER, STERN and VENDRYES, Bull. Soc. de pédiat. de Paris **36**:132 (March) 1938.

A boy aged 15 years had a funnel-shaped chest. He was very tall. There was hypertrophy of the genitalia. His mentality was somewhat retarded. He showed slight hyperglycemia but no glycosuria. The Hecht test was positive. Apparently he suffered from pituitary dysfunction in addition to congenital syphilis.

BENJAMIN, Montreal, Canada.

PNEUMOGRAPHIC EXAMINATION OF THE ANTERIOR MEDIASTINUM IN THE DIAGNOSIS OF ATYPICAL FORMS OF HYPERTROPHY OF THE THYMUS. R. PEREIRAS and A. CASTELLANOS, Arch. de med. inf. **7**:327 (July) 1938.

The authors claim that roentgenograms are sufficient in diagnosing typical forms of hypertrophy of the thymus but are inadequate for the atypical forms (vascular types). They have found pneumographic examination of the anterior mediastinum useful and innocuous. SCHLUTZ, Chicago.

Diseases of the Muscles, Bones, Joints and Lymph Glands

HETEROTOPIC BONE FORMATION. A. B. WALLACE, Tr. Med.-Chir. Soc. Edinburgh, 1938, p. 186; in Edinburgh M. J., October 1938.

Wallace presented 2 cases of heterotopic bone formation. One of the patients was a little boy aged 5½ years, brought into the hospital immediately after a crushing injury incurred between a wall and an automobile. Within a few hours blood was seen at the urethral meatus, extensive bruising in the groins and inner side of the thighs and a fulness of the angle between the scrotum and the left thigh. Urination remained difficult, but there was no further hematuria. The bladder became distended, and a roentgenogram showed evidence of separation of the symphysis pubis. There was no fracture, but probably the ligaments of the sacroiliac joint were torn. Four weeks later dribbling of the urine was taking place, and a roentgenogram showed dense calcifications at the symphysis pubis and below the left sacroiliac joint. Digital examination in the rectum revealed a hard mass on the left side. There existed marked relaxation of the left side of the neck of the bladder.

The injury must have caused a rupture of the external sphincter, a large hematoma and finally formation of a calcium deposit interfering with bladder function. NEFF, Kansas City, Mo.

TREATMENT OF OSTEOMYELITIS DURING THE PERIOD OF GROWTH. M. FÉVRE, Arch. de méd. d. enf. **41**:695 (Nov.) 1938.

In an exhaustive treatise on the classic type of osteomyelitis of infancy and childhood the author discusses the present conception of this disease, its clinicoanatomic varieties and the advances made in treatment. His conclusions are:

1. It is necessary to preserve an attitude of surgical eclecticism in osteomyelitis.
2. Primary septicemic forms should not be treated surgically.
3. One should withhold operative intervention until a well localized focus of suppuration appears. AMESSE, Denver.

RELAPSES IN OSTEOMYELITIS OF STAPHYLOCOCCIC ORIGIN. P. LOMBARD, Arch. de méd. d. enf. **41**:726 (Nov.) 1938.

In its inevitable tendency to become chronic, with alternate periods of calm and of activity, staphylococcic infection may well be compared with tuberculosis. This characteristic is particularly noticeable in osteomyelitis, whose victims may be subject to repeated and unexpected attacks over many years. Lombard reports such observations in 10 subjects varying in age from 5 to 18 years. He concludes that, far from acquiring immunity, local or general, some patients seem to show increased sensibility, an observation which leaves one frankly skeptical of the reports of successful vaccination against staphylococcic infections. AMESSE, Denver.

A Typical Case of Malformation of the Fifth Lumbar Vertebra, with Roentgenogram and Photograph. Nageotte-Wilbouchewitch, Bull. Soc. de pédiat. de Paris **36**:273 (April) 1938.

A girl 17 years old had a wedge-shaped fifth lumbar vertebra, as a result of which there was tilting of the pelvis and scoliosis of the lower part of the spine. She also had some prognathism and malocclusion, which were improved by orthodontic measures.

Benjamin, Montreal, Canada.

Is There a Uniform Heredity in Progressive Muscular Dystrophy? S. Kostakow and K. Bodarwé, Deutsches Arch. f. klin. Med. **181**:611 (March 19) 1938.

Kostakow and Bodarwé point out that whereas it is agreed by most investigators that progressive muscular dystrophy is hereditary, there is still controversy as to the mode of transmission. They have concluded, after careful study of the literature and investigations of several groups of families, that progressive muscular dystrophy is always hereditary. Mutations of the hereditary factors of past generations is the pathogenic basis. The hereditary transmission is not uniform. This lack of uniformity is due to the fact that, in addition to dominant genes, recessive genes play a part. There are two genotypically different forms of progressive muscular dystrophy, an infantile and a juvenile, both of which are hereditary. The authors show six genealogic trees and list the characteristics of the persons indicated in the diagrams. Two of the family group showed the hereditary transmission to be sex linked and recessive. Four other groups showed the transmission to be of the simple recessive type. In one genealogic tree with recessive heredity a marriage between blood relatives was detected in the ascendancy. In this connection the authors direct attention to the significance of marriages between relatives for the development of progressive muscular dystrophy from a recessive hereditary factor. In the genealogic trees with the sex-linked recessive heredity most of the patients had the infantile type, with pseudohypertrophy; in trees with the simple recessive heredity there were patients with the infantile and patients with the juvenile form. The causes of death were usually disorders of the respiratory organs; in the patients who survived there was likewise great susceptibility to diseases of the respiratory organs.

Editor's Abstract. [Arch. Neurol. & Psychiat.]

Significance of Creatinuria in Progressive Muscular Dystrophy. P. Netolitzky and E. Pichler, Wien. Arch. f. inn. Med. **32**:121 (March 31) 1938.

Netolitzky and Pichler demonstrate that the administration of aminoacetic acid to patients with progressive muscular dystrophy causes an increase and later a decrease in the elimination of aminoacetic acid without necessarily effecting clinical improvement. They show further that malaria treatment of these patients may be followed by clinical improvement without there being essential changes in the elimination of creatine. Thus improvement in creatine tolerance is no measure of functional improvement of the dystrophic musculature. Nothing definite is known about the mechanism of creatinuria, but recent investigations have disclosed that whenever creatinuria is produced experimentally the muscular glycogen is in a state of decomposition. On the other hand, all factors which cause disappearance of the muscular glycogen result in creatinuria. From this the conclusion is drawn that creatinuria is a sign of the disappearance of glycogen from the skeletal musculature. Moreover, it appears that the connection between creatinuria and the disappearance of glycogen applies also to progressive muscular dystrophy and that the resynthesis of creatine and phosphoric acid to phosphagen is impaired. Thus, the conditions may be similar to those which exist in poisoning with monoiodoacetic acid. In such poisoning the blockage of the carbohydrate metabolism leaves no energy for the resynthesis of phosphagen, and finally the stores of phosphagen are

entirely depleted. The authors decided to study the fate of the creatine thus liberated, hoping that the results might permit conclusions in relation to progressive muscular dystrophy. In experiments on rabbits they showed that creatine appears only as a result of the intoxication; they think that this suggests that creatine is eliminated because its resynthesis is made impossible by the metabolic disorder elicited by the poisoning. Thus, the creatinuria appears as the result of the impaired relation of free and combined creatine. Whether this mechanism has a part in the creatinuria of progressive muscular dystrophy is still problematic.

J. A. M. A.

ANIRIDIA CONGENITA; IRIDEREMIA. E. M. NEHER, Am. J. Ophth. **21**:293 (March) 1938.

After a discussion of aniridia and a presentation of genealogic studies, Neher gives the following summary:

"The part of the aniridic family tree upon which accurate data could be obtained has verified the Mendelian inheritance law; that is, one half of the offspring possess the dominant character—aniridia—while the other half possess a normal iris. Furthermore, when the aniridic offspring are mated with normal individuals and have children, 50 per cent are aniridic and the remainder have a normal iris; but the normal offspring who marry normal individuals never have borne children with aniridia. The amount of iris present varies from complete aniridia to a small coloboma of the iris."

REESE, Philadelphia. [ARCH. OPHTH.]

THE PRESENT STATUS OF SHOCK AND FEVER THERAPY IN OPHTHALMOLOGY. S. C. HOWELL, South. M. J. **32**:208 (Feb.) 1939.

Howell states that shock or fever therapy, however produced, is a valuable form of treatment for ophthalmic disease. It has produced gratifying results in nearly all forms of acute and chronic infectious and inflammatory manifestations of the eye and its adnexa.

While innumerable reagents may be used to produce the reaction, boiled milk and typhoid vaccine are probably the most acceptable. From 5 to 10 cc. of boiled milk for intramuscular use and vaccine containing from 10,000,000 to 20,000,000 killed bacteria for intravenous use appear to be ample initial doses for the average 150 pound (68 Kg.) adult. An increase of approximately 50 per cent over the first dose is necessary to produce a similar reaction from the second dose.

Although the exact means by which improvement is obtained is not known, it is probable that both the formation of antibodies and the production of fever are valuable factors.

For the control of dosage, the amount of elevation of temperature is a satisfactory index of the amount of body reaction.

Moderate reactions, producing a temperature of approximately 102 F., produce maximal results.

SCHLUTZ, Chicago.

APLASIA OF THE OPTIC NERVES. H. RIDLEY, Brit. J. Ophth. **22**:669 (Nov.) 1938.

This rare anomaly was seen in a child 1 year of age. The child did not follow light. There was no nystagmus. The anterior portions of the eye were normal. The pupils were inactive to light but varied in size from time to time, irrespective of stimulus. The media were clear. The fundus reflex was pale red. In place of the optic nerve head there was a deep excavation, the floor of which was about 5 diopters beyond the level of the fundus. Its color was gray. From the floor of the pit emerged only minute threads, representing retinal vessels, the lower branch in the right eye being the only one which contained more than a trace of blood, and even this appeared to fade out soon after leaving the edge of the excavation.

The article is illustrated.

ZENTMAYER, Philadelphia. [ARCH. OPHTH.]

SYNDROME OF BLUE SCLEROTICS (VAN DER HOEVE). J. S. CHARAMIS, Ann. d'ocul. **175**:738 (Oct.) 1938.

Charamis states that for the first time in Greece it has been possible to study four generations in one family in which many members presented the van der Hoeve syndrome, either partial or complete.

This syndrome presents three classic symptoms: blue scleras, multiple fractures and otosclerosis. The first report of the constitutional predisposition of certain persons to fractures was that of Lobstein, in 1829. Eddowes in 1901 reported that blue scleras are often present in such persons. He also demonstrated the familial and hereditary character of the condition. In 1916 van der Hoeve and Klein added deafness as the third principal symptom. Practically all authors are agreed that the condition is familial and inherited.

In the family studied here persons in perfect health had descendants who presented the syndrome in part. Certain families may present one of the three symptoms, such as deafness or blue scleras or bone fragility, or two of these symptoms. In the family described here the males seemed to be more afflicted than the females.

The four generations are described in detail.

McKEE, Montreal, Canada. [ARCH. OPHTH.]

Diseases of the Eye

OPERATION IN A CASE OF MARCUS GUNN PHENOMENON. A. OFFRET and G. OFFRET, Bull. Soc. d'opht. de Paris **50**:61 (Feb.) 1938.

The family of a girl of 9 years insisted that an operation be done for ptosis of the right eyelid. The eyelid covered a greater part of the cornea and was accompanied by limitation of the elevation of the globe. When the mouth opened in mastication the lid raised, only to return to the original position when the mouth was closed. The operation used has been described by Nida (*Ann. d'ocul.* **166**:639, 1929). It consists in inserting the tendon of the superior rectus muscle into the tarsus of the upper lid. Two and one-half years after operation the child's lid still remained motionless when the mouth was opened. There was also no movement of the lid on mastication. A bibliography accompanies the article.

L. L. MAYER. [ARCH. OPHTH.]

MELANOSIS RETINAE. G. CIOTOLA, Ann. di ottal. e clin. ocul. **66**:543 (July) 1938.

Forty cases of melanosis retinae are recorded in the literature. Two typical cases are reported. One of the patients was a girl of 15 years and the other a woman of 26. Both patients had normal vision and normal visual fields. The only ocular findings were peculiar areas of grouped pigment deposits in the deeper layers of the retina. The retinal vessels and the retina around and between the spots were normal. In the first patient both eyes were affected; in the second, only the right eye. In nearly all of the reported cases the condition has been stationary with no effect on vision. The only report of sections is that of Parsous, who found an accumulation of cells in the pigmented epithelium in the affected areas. The author reports on sections of an eye removed for melanosarcoma. The fundus had not been observed during life, but aside from the tumor, marked thickening of the pigmented epithelium in certain peripheral portions of the retina was present, which he believes may represent the same condition. He points out that the condition is in the retina itself and is to be differentiated from melanosis of the choroid, although in the sectioned eye this condition was also present.

Drawings of the fundi and sections accompany the article.

GIFFORD, Chicago. [ARCH. OPHTH.]

PHLYCTENULAR DISEASE IN SHANGHAI. P. C. KWAN, Chinese M. J. **54**:421 (Nov.) 1938.

In China this disease, while less prevalent than trachoma, is also serious and the cause of blindness in a high percentage of cases. The patients are mostly young adults—males 16 to 20 years old and females 16 to 30. The disease is more common in males. Among children, the group next most frequently involved, the patients are from 1 to 5 years old. The youngest subject was 2 months old.

Ulceration is frequent among children, affecting the corners of the eyelids, notably the external canthus, especially when the organism is the Morax-Axenfeld diplobacillus—to a less extent when it is the Koch-Weeks bacillus. Many of the children at first had regular yearly attacks, then became free for some years and during adolescence had a recurrence. Kwan states that in Europe or America the disease is most common in childhood. A series of patients was tested with a low dilution of tuberculin, the Mantoux technic being used, and the results were almost universally positive.

Kwan found that the most important goal in treatment is to prevent recurrence, and he recommends the method of Preston and Savin, i. e., the administration of tuberculin to patients who have positive reactions to tuberculin. Foci of infection, such as those in tonsils and teeth, must be corrected. The improvement of the diet, especially in poor families, who use polished rice, salt fish and pickled vegetables, is a necessity, especially with regard to assuring an adequate intake of vitamins. The intake of protein is deficient in many of these patients, who do not have meat in their diet. Soy beans are recommended in China as a valuable addition, available to people of that country.

NEFF, Kansas City, Mo.

Skin Diseases; Allergy

TREATMENT OF INFANTILE ECZEMA. L. W. HILL, J. A. M. A. **111**:2113 (Dec. 3) 1938.

The group of eruptions in infancy, including seborrheic, atopic, contact and mycotic dermatitis, make up the eczematoid dermatoses. The atopic or allergic forms and the seborrheic are the common forms. Prescriptions are included for the local treatment of these conditions. Dietary treatment of seborrheic forms includes chiefly the avoidance of obesity; that of the atopic forms, the elimination of the allergen. Skin testing is advised to determine, if possible, the offending food. Environmental substance must be kept in mind. None of this therapy cures the condition, and often the treatment does not even alleviate it.

HEERSMA, Kalamazoo, Mich.

ALLERGY IN CHILDHOOD: III. ITS ONSET AND NATURAL PROGRESS. B. RATNER, J. A. M. A. **111**:2345 (Dec. 24) 1938.

In analyzing the onset and natural progress of allergy in childhood Ratner found that 50 per cent of 200 patients had an onset in the first year of life. The family tendency did not greatly influence this. Eczema was by far the most common initial manifestation, with most of the eczematous children showing positive skin reactivity to foods, inhalants and contactants. Some of this sensitivity may have been acquired in utero. Asthma may follow eczema or it may be the first manifestation of allergy, in most cases about the third or fourth year. Urticarias appear at various ages and hay fever chiefly after 6 years of age.

The importance of inhalants even in allergy other than hay fever and asthma is stressed, as is the presence of sensitivity to multiple allergens in all of these conditions.

HEERSMA, Kalamazoo, Mich.

TREATMENT OF INFANTILE ECZEMA. M. B. SULZBERGER, J. A. M. A. **112**:38 (Jan. 7) 1939.

Sulzberger classifies the infantile eczemas into eight groups which are similar to Hill's four groups, i. e., contact, atopic, seborrheic, parasitic, physical, circum-

scribed neurodermatitic, uncertain as to origin, and mixed. He gives several reasons for the difference in cutaneous response in infants. After attempts to cure or ameliorate the condition by dietary and environmental means, treatment becomes that of the dermatologist. Here Sulzberger outlines the required procedures—removal of cysts, drying or powdering, application of parasiticides, application of ointment of coal tar N. F. and soothing lotions, care of oozing and weeping and prevention of scratching. The principal drugs recommended are coal tar N. F., other tars, mercurials, resorcinol and sulfur.

HEERSMA, Kalamazoo, Mich.

TREATMENT OF INFANTILE ECZEMA: FROM THE POINT OF VIEW OF THE ALLERGIST. B. Z. RAPPAPORT and R. HECHT, J. A. M. A. **112**:317 (Jan. 28) 1939.

Contact and atopic types of infantile eczema are discussed by Rappaport and Hecht from the immunologic standpoint.

After emphasizing the importance of a careful, complete history, they describe the patch, cutaneous scratch and intracutaneous tests for allergens. The relative frequency of the allergies in infancy is given. Their evaluation is a matter of experience. Other means of diagnosis are environmental studies, elimination of suspected foods and determination of passive transfer antibodies. In cases of atopic inheritance special procedures are required as prophylaxis. The authors briefly mention treatment directed along these lines.

HEERSMA, Kalamazoo, Mich.

TWO FAMILIES SHOWING HEREDITARY ECTODERMAL DYSTROPHIES. C. HARDWICK, Brit. J. Dermat. **51**:24 (Jan.) 1939.

Two families are discussed, the first with hyperkeratosis subungualis and the second with hypotrichosis et dystrophia unguium.

RATTNER, Chicago. [ARCH. DERMAT. & SYPH.]

ARTERIAL CALCIFICATION AND SUBCUTANEOUS CALCINOSIS: CASE SHOWN IN JANUARY 1936. J. H. SHELDON, Proc. Roy. Soc. Med. **31**:1119 (July) 1938.

When previously shown at the age of 22 months the patient exhibited marked calcification of the iliac and femoral arteries roentgenographically; also subcutaneous deposits of calcified material in the legs and around one elbow. The appearance suggested hypothyroidism, and the blood counts revealed anemia associated with lymphocytosis.

Subsequently the deposits of calcium in both the arteries and the subcutaneous tissues slowly decreased, and roentgenograms at the time of writing were entirely negative. A photograph of the child at 17 months suggests cretinism. When the patient was first seen cretinism was not considered. Subsequently his appearance became more suggestive of this condition, and in June 1936 he was given thyroid, ¼ grain (0.016 Gm.) a day. Improvement in the general condition followed. The dose was increased, but the child became irritable and suffered from insomnia. The administration of thyroid was discontinued for five weeks, and the effect was gradual loss of appetite, coldness of the extremities and a tendency toward protrusion of the tongue. Immediate improvement followed readministration. There seems to be little doubt, therefore, that the child had subthyroidism of moderate degree.

WILLIAMSON, New Orleans.

PINK DISEASE. S. N. JAVETT, South African M. J. **12**:881 (Dec. 10) 1938.

Javett reviews the literature on acrodynia along the usual lines and reports cases. He states that he has seen 2 cases in which prontosil (form not specified) was given without benefit.

GONCE, Madison, Wis.

CALCIFIED AND MUMMIFIED EPITHELIOMAS OF THE SKIN IN CHILDREN. M. FÈVRE, R. HUEGUININ and F. VELIZ PAIZ, Arch. de méd. d. enf. **42**:73 (Feb.) 1939.

Epitheliomas of this type are benign in their evolution but have many unsolved features in their pathogenesis. After operating in 7 cases, the authors made an exhaustive study of tumors of the skin in young subjects. They believe these growths to be much more common than is generally considered, especially in early life; one report concerns an infant of 3 months, and six reports in the literature concern nurslings varying in age up to 6 months. The development of the epithelioma is insidious; the evolution is extremely slow and entirely free from pain; the tumor is slightly more frequent in females. The discovery of the tumor is usually quite accidental. The essential characteristics are: great induration, adherence to the skin and total absence of involvement of the deeper tissues. The site of the tumor is practically always either the face or the neck, but cases have been reported in which the growth involved the arm or the leg. Ulceration of the skin may occur, with discharge of calcareous material. Recurrent tumors have been observed, but multiple growths are rare. A full discussion of the histologic observations, chemical characteristics and treatment follows.

AMESSE, Denver.

A MALIGNANT TYPE OF ACRODYNIA. L. CAUSSADE, J. WATRIN and N. NEIMANN, Arch. de méd. d. enf. **42**:91 (Feb.) 1939.

Up to this time, the aspect of malignancy has never been considered in the study of acrodynia. The investigations of Marquezy and Ladet have called attention to a particularly severe type of this disease in the eastern part of France. Four cases are reported in children varying in age from 16 months to 6 years; all were similarly affected: After a period of several weeks the benign invasion suddenly assumed alarming features, the brunt of the attack being borne by the nervous system in the form of asthenia, adynamia and unconsciousness, with corresponding changes in expression and great disturbances in the circulatory and respiratory systems. Later on, the digestive apparatus was attacked, but no visceral symptoms were noted in any case. Three deaths occurred in this series, and autopsy disclosed striking changes in the tissues of the brain and sympathetic system.

AMESSE, Denver.

CUTANEOUS FAMILIAL INFANTILE GANGRENE. J. URUENA, Bull. Soc. franç. de dermat. et syph. **45**:864 (May) 1938.

Gangrene of the skin of infants has been described under numerous titles, the multiplicity of which indicates the diverse causes of the condition. Gangrene of infants, in contrast to that of adults, is rarely on a strict vascular basis and is not especially localized to the extremities. Infantile gangrene is usually due to microbic infection from without or within the body (septicemia). In general there are two varieties:

1. *Primary.*—This type occurs most often in cachectic subjects, such as those with enteritis, suppurations or tuberculosis. It frequently begins with hemorrhagic bullae which become gangrenous, as deep nodules or as ordinary impetigo. The buttocks, thighs and neck are favorite sites. The usual course is characterized by fever, diarrhea, vomiting, convulsions and death. Various bacteria may be causative (streptococci, staphylococci, Proteus vulgaris, Bacillus perfringens or Bacillus ramosus).

2. *Secondary.*—This type accompanies eruptive diseases, such as variola, varicella, measles, urticaria, mycoses, leukemia, erythema nodosum and erysipelas, in infants of low resistance. The patients are frequently tuberculous or syphilitic. Almost always the prognosis is grave. The author reports 2 cases of cutaneous gangrene, the patients being brother and sister. The condition was classed in the first group and in each instance was preceded by enteritis.

LAYMON, Minneapolis. [ARCH. DERMAT. & SYPH.]

ASCORBIC ACID CONTENT OF DISEASED SKIN. H. ROTTER, Ztschr. f. Vitaminforsch. **8**:24, 1938.

By the use of Rotter's method for estimating the amount of ascorbic acid in the skin it was shown that in different cutaneous diseases the affected part of the skin may contain a different amount of ascorbic acid as compared with the normal skin adjacent to it.

ARON, Chicago.

ACRODYNIA. J. BOGDANOWICZ, Pediatria polska **18**:214 (April) 1938.

Acrodynia is rare in Poland. Only 10 cases have been reported. Acrodynia is known as Selter's, Swift's or Feers' disease and was described by these men. It occurs in children from 2 to 5 years of age, mostly in the summer and fall. The condition responds to vitamins C and A and a diet high in protein and fat.

KRUPINSKI, Chicago.

EXPERIMENTAL STUDIES ON CONGENITAL ALLERGY. M. YAMAMOTO and Y. HAMAMOTO, Orient. J. Dis. Infants **23**:487 (May) 1938.

Yamamoto and Hamamoto studied the effect of sensitization of pregnant guinea pigs. Sensitization was obtained by injecting horse serum approximately two weeks before delivery. Using the Schultz-Dale technic, they were able to demonstrate: (1) passive diaplacental immunization, in which the allergic antibodies were transmitted in utero; (2) active diaplacental immunization, in which the allergens were transmitted through the placental membranes, and (3) sensitization of the newborn by the allergen excreted in the breast milk.

The authors infer from these observations that transmission of allergy from a sensitized mother to her offspring can take place, the resultant condition of the offspring being known as congenital allergy.

KATO, Chicago.

SERUM DISEASE. T. HALBERTSMA and G. W. HYLKEMA, Maandschr. v. kindergeneesk. **8**:32 (Oct.) 1938.

Of 524 children with diphtheria who were treated with serum, serum diseases developed in 177. The larger the doses of serum injected, the greater the probability that the child will experience serum disease. Of the children who were given large doses of serum, 12 fell seriously ill and showed a relapse of the exanthem.

VAN CREVELD, Amsterdam, Netherlands.

TREATMENT OF VERRUCAE. P. J. VAN PUTTE, Nederl. tijdschr. v. geneesk. **82**: 5737 (Dec. 3) 1938.

Putte describes a simple treatment of verruca vulgaris, verruca plana juvenilis and condyloma which, according to his experience, is most effective.

VAN CREVELD, Amsterdam, Netherlands.

TREATMENT OF PSORIASIS. T. M. LEEUWEN, Nederl. tijdschr. v. geneesk. **82**:5750 (Dec. 3) 1938.

Leeuwen enumerates the medicines and methods of treatment which he applies in dealing with psoriasis and demonstrates how he has come to choose among the various external applications by his experience of their activity and usefulness. In each case special attention must be paid to the influence on constitutional trends of such factors as habits and diet, though this influence is not yet amenable to analysis.

VAN CREVELD, Amsterdam, Netherlands.

Miscellaneous

INTRAVENOUS INJECTION OF HYPOTONIC SALT SOLUTION CONTAINING SULFANILAMIDE FOR STREPTOCOCCIC MENINGITIS. G. M. RETAN, Am. J. Dis. Child. **56**:483 (Sept.) 1938.

In experiments on monkeys, planned to determine whether giving sulfanilamide intravenously has the advantage of increasing the concentration of the drug in the cerebrospinal fluid, Retan observed that when physiologic solution of sodium chloride containing sulfanilamide is given to monkeys intravenously the concentrations of sulfanilamide are greater in the blood than in the cerebrospinal fluid. When a hypotonic solution of sodium chloride containing sulfanilamide is injected intravenously, the concentrations during the first injection are the same as with the physiologic solution. However, if the injection of a hypotonic solution is repeated on the second day there occurs a shift to a higher percentage of sulfanilamide in the cerebrospinal fluid than is contained in the blood. A similar shift to a higher concentration in the cerebrospinal fluid than in the blood can be produced by giving the drug by mouth in solution or in capsules prior to the intravenous injection of a hypotonic solution of sodium chloride. The shift depends on the presence of sulfanilamide in the tissues of the body and the intravenous introduction of a hypotonic solution of sodium chloride containing sulfanilamide. The author is not in a position to know what result he would have obtained in his case of hemolytic streptococcic meningitis had he given sulfanilamide by mouth and by subcutaneous injection without using injections of hypotonic solution of sodium chloride containing sulfanilamide. There was prompt subjective and objective improvement within an hour after the beginning of each intravenous injection. The doses of sulfanilamide used in the intravenous solution (from 6 to 10 Gm. in twenty-four hours) were unnecessarily large. An alkaline powder of calcium carbonate and sodium bicarbonate was given at intervals of four hours. The rate of injection most successfully used is 10 cc. of solution each hour per pound of body weight. A 0.375 per cent solution has been found to be most effective. Treatment for five hours with rest intervals of several hours between treatments is advised. Cerebrospinal fluid is released from the lumbar puncture needle during the intravenous injection for the purpose of relieving increased intracranial pressure. If the fluid is under considerable pressure and is spurting from the needle, it is wise to drain from 5 to 10 cc. during half an hour. If the fluid is dripping rapidly, less than this amount should be drained. If the fluid emerges from the needle by a slow drop the stylet should be replaced at once without draining any fluid.

EDITOR'S ABSTRACT. [ARCH. NEUROL. & PSYCHIAT.]

SULFANILAMIDE IN TREATMENT OF BRAIN ABSCESS AND PREVENTION OF MENINGITIS. P. C. BUCY, J. A. M. A. **111**:1639 (Oct. 29) 1938.

Bucy reports a case in which an abscess of the brain was cured and almost certain hemolytic streptococcic meningitis prevented by the administration of sulfanilamide. Owing to an error in diagnosis, a right cerebellar abscess was exposed with a bilateral suboccipital craniectomy. The contents of the abscess were aspirated, and the surface of the cerebellum was contaminated with pus swarming with hemolytic streptococci, the ventricular system and the subarachnoid space being thus exposed to this infection. The abscess was not drained. The administration of sulfanilamide was begun at once. The patient improved steadily. There was almost no febrile reaction, and at no time did signs either of meningitis or of refilling of the abscess develop. The patient had almost completely recovered within two weeks.

EDITOR'S ABSTRACT. [ARCH. NEUROL. & PSYCHIAT.]

TREATMENT OF PNEUMOCOCCIC MENINGITIS. M. FINLAND, J. W. BROWN and A. E. RAUH, New England J. Med. **218**:1033 (June 23) 1938.

Of 99 patients with pneumococcic meningitis, none recovered except 6 of the 10 who were treated with sulfanilamide alone or with serum. The procedure adopted was as follows: 1. Complete and frequent drainage of the spinal fluid was carried out. 2. Continuous large doses of sulfanilamide were given by mouth or by subcutaneous injection, if necessary, immediately. The optimal dose has not been determined. Sodium bicarbonate was given with each dose. 3. The pneumococcus was identified as rapidly as possible, and sufficient specific antipneumococcus serum was given intravenously to establish a balance of antibody in the circulating blood. 4. Moderate intake of fluid was maintained. 5. About two hours after a reasonable dose was given, blood was withdrawn, and the serum was separated. 6. At the time of the next lumbar puncture this serum was given intraspinally (from 5 to 10 cc.). 7. Lumbar punctures were repeated until the fluid was normal. The frequency was determined by the initial pressure of the fluid and its cellular and protein contents. 8. After the first week of sulfanilamide therapy, if anemia developed, transfusions were given and were repeated as necessary until the drug was discontinued (after from seven to fourteen days, on which the spinal fluid was sterile). Such procedures serve to insure a balance of antibody in the blood stream and to control the bacteremia. They should in most instances in which the sulfanilamide effectively reduces the infection, provide an adequate amount of antibody and complement in optimal proportions and in a medium which is likely to give the least local or general reaction and the greatest antibacterial effect.

EDITOR'S ABSTRACT. [ARCH. NEUROL. & PSYCHIAT.]

PROGRESSIVE FACIAL PALSY PRODUCED BY INTRATEMPORAL EPIDERMOIDS. G. JEFFERSON and A. A. SMALLEY, J. Laryng. & Otol. **53**:417 (July) 1938.

During the last five years Jefferson and Smalley encountered 6 patients in each of whom slowly progressive facial palsy was proved to be due to an epidermoid lodged within the temporal bone. No infection was present in any of them, and 3 patients had never had otitis media. All, however, were deaf to a greater or less degree on the side of the palsy, and this fact led to a painstaking investigation of the temporal bone for a possible causative lesion. The facial paralysis had in each case taken several months to develop and was in that respect totally unlike Bell's palsy. The syndrome is related to the pure pressure effect of an epidermoid and not to any septic condition such as accompanies the ordinary cholesteatoma.

EDITOR'S ABSTRACT. [ARCH. NEUROL. & PSYCHIAT.]

PARAAMINOBENZENESULFONAMIDE [SULFANILAMIDE]. A. J. ABALLI, Arch. de med. inf. **8**:1 (March) 1939.

Aballi gives an excellent review of the history, pharmacology, physiology and therapeutics of sulfanilamide as an introduction to the other articles on this drug that appear in this issue. There is an excellent bibliography.

SANFORD, Chicago.

PROCEEDINGS OF THE GERMAN PEDIATRIC SOCIETY—WIESBADEN, 1938. Monatschr. f. Kinderh. **75**:1 (Sept.) 1938.

The 1938 session of the German Pediatric Society was as startling as the one in the previous year. The session was opened by Hamburger, of Vienna, who expressed the enthusiasm of all Austria at being able to give up its identity and become Germany. "Heil Hitler" was a feature, and one gets the impression that Hitler has become the dean of German pediatricians. The topics presented in the papers may be stated briefly:

1. Convulsions in children are due to epilepsy or spasmophilia.

2. Epilepsy may be congenital or acquired; the latter type is often acquired through injury sustained at birth.

3. Roentgen treatment of the head is of value in controlling epileptic convulsions.

4. As regards the future of children with birth injuries, if one uses the presence of bilirubin in the spinal fluid and blood serum as a diagnostic sign the prognosis is practically as good as for a normal control group. In other words, there were just as many debilitated and idiotic children in a group of 140 normal infants as in the group with cerebral hemorrhage, as judged by the bilirubin test.

5. Convulsions not only result from injury of the brain but cause injury of the brain; thus every effort should be made to prevent them.

6. The apple treatment of diarrhea is recommended.

7. Cutaneous lesions resembling lichen urticatus may result from bedbug bites.

8. When two simultaneous Mantoux tests are made with dilutions of 1: 10,000 and 1: 1,000,000, some children react much more strongly to the larger dose; others react equally to both dilutions. The latter group requires special prophylaxis and should be kept under the closest observation. (This paper was read by von Groer, of Poland.)

9. In the realm of communicable diseases the organisms responsible for rubeola, epidemic parotitis and aphthous stomatitis had been isolated.

10. There was the usual group of studies on vitamin D and the shock treatment of rickets.

11. An unusual treatment of pylorospasm was announced in the form of retention enemas of freshly voided urine. In a nursing infant good results can be accomplished by the mother's taking twice daily enemas of 15 to 30 cc. of her own urine. This treatment is a specific!

GERSTLEY, Chicago.

Society Transactions

AMERICAN PEDIATRIC SOCIETY

CLIFFORD G. GRULEE, M.D., *President*

Annual Meeting, Skytop, Pa., April 27-29, 1939

HUGH MCCULLOUGH, M.D., *Secretary*

(Concluded from page 682)

Fourth Session

Friday Evening, April 28

ACUTE COCCIDIOIDOMYCOSIS WITH ERYTHEMA NODOSUM IN CHILDREN. DR. HAROLD K. FABER, DR. CHARLES E. SMITH (by invitation) and DR. ERNEST C. DICKSON (by invitation), San Francisco.

This is an acute disease caused by the fungus Coccidioides immitis and endemic in the San Joaquin Valley of California. Unlike the chronic disease, coccidioidal granuloma, caused by the same organism, it is common in children (but not confined to any age group), runs an acute course and uniformly ends in recovery. It is associated with hypersensitivity to the filtrable product of the fungus, coccidioidin. The disease begins with fever, generalized aching, headache, cough, sore throat and pleural pain lasting a few days. After an average interval of relative well-being, erythema nodosum appears, sometimes accompanied by acute arthritis and conjunctivitis. Roentgenograms of the chest at this time often show infiltrations around the hilus and in the pulmonary fields much like those seen with primary tuberculosis, to which the disease has several other points of resemblance. The diagnosis is based on the cutaneous reaction and on the recovery, by culture and animal inoculation, of the fungus from the sputum or stomach washings. The prognosis is favorable. No deaths have been reported. The acute disease is not known to have progressed into the chronic form, nor, with a single exception, has coccidioidal granuloma been found in a patient who had previously had acute coccidioidomycosis with erythema nodosum. The acute disease is self limited, and treatment is purely symptomatic.

DISCUSSION

DR. CLIFFORD G. GRULEE, Evanston, Ill.: Recently there has come from Wallgren's clinic some definite evidence that erythema nodosum is sometimes associated with rheumatic fever alone. The parallelism between the course of the fever in this case and the course with tuberculosis is evident.

Recently the president of the American Tuberculosis Association stated that a large proportion of the patients that showed calcium deposits in the lungs which would lead one to suspect tuberculosis had proved in certain localities to have negative tuberculin reactions, the percentage in many instances being as high as 25 to 35.

Are the calcium deposits which Dr. Faber mentions similar to those which are frequently associated with tuberculosis of the lung? Does he think that this coccidioidomycosis has extended beyond the limits of the San Joaquin Valley and of Arizona into different portions of the United States?

DR. HAROLD K. FABER, San Francisco: The conditions under which the coccidioides fungus grows are restricted and at present are known to exist only in the San Joaquin Valley and in certain parts of Arizona; however, when the subject has been more fully studied it is possible that other endemic foci will be found.

The calcium deposits in the hilar region are much like those of tuberculosis and evidently indicate the presence of residual lesions in the lymph glands. Personally I have not seen lesions like those of Ghon in the pulmonary fields in coccidioidomycosis. Such lesions have, however, been discovered post mortem, and from them the fungus has been recovered.

Concerning the cause of erythema nodosum, I believe that it is due to a state of specific hypersensitivity to the proteins of a number of different microorganisms, of which the two most definitely incriminated are the tubercle bacillus and the coccidioides fungus, as shown by the severe character of the cutaneous reactions to tuberculin and to coccidioidin, respectively. There is some reason to believe that erythema nodosum may also be caused by some streptococci by the causative agent, whatever it may be, of rheumatic fever.

While coccidioidomycosis may appear to be a disease of local rather than of general interest, I wish to repeat that the disease may be encountered almost anywhere in the United States in persons who have traveled in endemic areas and returned to their homes. In particular, fruit pickers migrate to California with their families from various points in the Middle West during the summer months and return after the harvest. Physicians in that part of the country should be on the watch for the disease.

Coccidioidin for cutaneous testing is not as yet generally available. It can be obtained on request from the Department of Public Health and Preventive Medicine, Stanford University Medical School, San Francisco.

MATERNAL AND CHILD HEALTH UNDER THE NATIONAL HEALTH PROGRAM. DR. MARTHA M. ELIOT, Washington, D. C.

If the proposed National Health Program outlined by the President's Interdepartmental Committee to Coordinate Health and Welfare Activities were to be made effective by Act of Congress, there would become available to the states increased grants for maternal and child health services, for other basic health and medical services and for hospital care. Present programs could be expanded gradually along lines already indicated through experience gained by the states under the administration of Title V of the Social Security Act. The experience in administration of the crippled children's program is particularly important in view of the recommendation to increase the authorization for appropriations for general medical care of children and medical care during maternity and infancy. The need for such expansion appears to be clear.

Because of their interlocking character and their implications for the maternal and child health program, each of the five recommendations of the President's Committee should be given consideration by pediatricians and obstetricians. The five recommendations concern general public health organization and maternal and child health; the construction of hospitals where needed; the provision of medical care, including hospital care, for the medically needy; plans to aid self supporting persons by spreading costs of care over periods and among groups of people, and, lastly, social insurance for disability compensation.

The recommendation for maternal and child health was that existing services under Title V of the Social Security Act be extended under a plan of gradual orderly expansion in the general field of health supervision and in two special areas—maternity care and care of newborn infants, and medical care of children. The development of basic local health organization is fundamental to development in the special field of maternal and child health and should precede it. To assure high quality of service in the special field, state and local administrative agencies will need to increase the number of pediatricians and obstetricians on their staffs

who are qualified to act as consultants; provide model teaching child health and prenatal conferences; develop facilities for expert diagnostic services; establish high standards of medical nursing and hospital care; develop cooperative arrangements with welfare departments, and seek the advice of pediatricians, obstetricians and other professional groups in the establishment and maintenance of the various professional services to be rendered. Finally, with reference to maintaining care of high quality, the committee specifically recommended the development of centers of postgraduate instruction for medical, nursing and medical-social personnel.

Increased funds would make it possible for state and local health agencies to increase payments to qualified physicians for medical and nursing care of women at delivery, as well as antepartum and postpartum care, and for care of children, to pay for hospital care, to provide a more nearly adequate number of public health nurses, to provide more health supervision through conferences and clinics and to provide social services as needed.

DISCUSSION

DR. HENRY F. HELMHOLZ, Rochester, Minn.: Dr. Eliot has given pediatricians a challenge in meeting a duty that we have to face, as individuals and as groups in the organizations represented here as well as in the American Academy of Pediatrics, and that we as a group will meet. This program is one for which we must prepare ourselves.

Dr. Eliot tells us that only 2.5 per cent of the children in the United States of America are being taken care of by pediatricians. We must realize how many children there are who are receiving practically no special pediatric care.

The Children's Bureau has accomplished much in the education of the general practitioner, and we shall have to look to him to carry out a large part of this program; but Dr. Eliot's address brings home to us, as nothing else has, our duties in helping to make this program a success.

DR. KENNETH D. BLACKFAN, Boston: Dr. L. Emmett Holt, in his second term as President of the American Pediatric Society, called attention to the necessity for three types of pediatricians: (1) the physician who is fundamentally trained to be a leader in university pediatric centers; (2) the well trained pediatrician who becomes a motive force in the betterment of health of children in the community, and (3) the pediatrician who clearly sees and accepts the responsibility for expansion of efforts through public health services to children.

Since those words were issued there has been an irregular response of pediatricians, who are becoming well fitted by education to accept the third responsibility. Tonight, because of our training we pediatricians stand at the forefront of an opportunity to help in this present era of federal, state and community responsibility for the betterment of the health and welfare of children in the United Sates.

Dr. Eliot has emphasized this third responsibility, this third opportunity for those who are interested in the welfare of children.

DR. DEWITT H. SHERMAN, Buffalo: Eight or ten years ago New York State took an active part in the consideration of the problems that Dr. Eliot has mentioned. The state health commissioner was then Dr. Herman Biggs; he was followed by Dr. Mathias Nichol. The state was divided into sections. There were obstetric and pediatric consultants. A great deal of work was done at that time, largely so along the lines that Dr. Eliot suggested. I should like to ask her why that effort collapsed and now amounts to nothing.

DR. MARTHA M. ELIOT, Washington, D. C.: Dr. Sherman, did you refer to the work of the New York State Department of Health?

DR. DEWITT H. SHERMAN, Buffalo: Yes.

DR. MARTHA M. ELIOT, Washington, D. C.: I cannot agree that the maternal and child health program has collapsed entirely and amounts to nothing. A considerable program is going on in the field of child health. Possibly it is not the type of program that developed under Dr. Biggs; I am not familiar with the program that he introduced. However, a considerable program is now being built up on the district basis rather than on the statewide basis.

The present commissioner of health of New York State, Dr. Godfrey, realizing that the state and the population are large, is inaugurating a district system of health supervision; as time goes on the maternal and child health work of the state will be more and more developed through that decentralized system. The department of health is planning to have directors or assistant health officers in each of the seventeen districts. Each assistant district health officer will presumably undertake a maternal and child health program similar to that which the smaller states have undertaken on a statewide basis.

IMMUNOLOGIC RELATIONS BETWEEN COW'S MILK AND GOAT'S MILK. DR. LEWIS WEBB HILL, Boston.

Some infants hypersensitive to cow's milk can take goat's milk without harm, and some cannot. It has been well established that the caseins of the two types of milk are immunologically identical. It is stated many times in the literature that the lactalbumins are immunologically species specific. These statements, however, are not based on original work. The only original work on the subject was done by von Versell in 1915; he found that while cow's and goat's lactalbumin showed greater immunologic differentiation than did cow's and goat's casein, they were by no means entirely species specific.

Forty-four eczematous infants who gave a positive intracutaneous reaction to cow's lactalbumin were tested with goat's lactalbumin. Ten had negative and 9 had doubtful reactions, and 25 gave as strongly positive reactions to goat's as to cow's lactalbumin. The species specificity of the two lactalbumins is not as great as has generally been believed.

In apparent contradiction to these results is the fact that most infants with the severe type of sensitivity to cow's milk, who go into shock when they take even small amounts, can take goat's milk with impunity. In 25 collected cases the 15 babies who were given goat's milk took it without harm. As a rule these infants do not have eczema, and in spite of exquisite clinical hypersensitivity to cow's milk they are not likely to give positive cutaneous reactions. These patients are uncommon, and concerning their immunologic states there are but few available data. Such data as there are suggest that their immunologic state more closely resembles that of the anaphylactic animal than it does that of the patient with asthma, hay fever or eczema. This may explain why the children have sharply defined sensitization to the species-specific factor of cow's lactalbumin alone, for it has been thought that the anaphylactic antibody is more highly specific and less likely to react with closely related antigens than is the atopic reagin characteristic of asthma, eczema and hay fever.

DISCUSSION

DR. CHARLES G. KERLEY, New York: Nine cases of so-called shock came under my observation.

A child 8 months of age took 2 ounces (59 cc.) of milk; this was followed by shock, collapse and death after seventeen hours. Another patient nearly died in my office, after a trial with 9 drops of cow's milk on the tongue; the child was resuscitated with much difficulty. The other patients were made violently ill through ingestions of cow's milk, which necessitated other means of nourishment. Five were successfully fed with goat's milk. I had 2 patients with eczema who reacted to the cutaneous scratch test for sensitivity to cow's milk—an unusual circumstance.

DR. FRITZ B. TALBOT, Boston: One phase of this subject is not usually sufficiently emphasized; that is the conditions that favor making a child sensitive to a foreign protein.

If it is desired to sensitize an animal to a foreign protein, the protein is injected at intervals of ten days.

Under certain circumstances one can make a child sensitive by exposing him at similar intervals. From that the following lesson can be learned: If a new food is started, it should be given more frequently than once in ten days; once every other day is better.

The children who run the greatest risk of becoming sensitive are those who have a family history of sensitization resulting in such a condition as hay fever or asthma.

Such histories are too often neglected. The diets of these children ought to be considered in terms of the level of their immunity to foreign protein.

I want to emphasize that many of these children will be able to ingest protein for a while and then will have a gastrointestinal upset, which will allow foreign proteins to pass through the intestinal mucous membranes into the blood unchanged.

Dr. Oscar M. Schloss, New York: The great majority of children who suffer from stormy symptoms the first time a food such as cow's milk or egg is ingested are apt to have an immunologic reaction different from the reaction of those who suffer from asthma or hay fever. Such patients may not have a positive cutaneous reaction to the offending food, but in some cases the reaction is definitely positive. I am not sure that the failure of a young infant to react is not due to the well known general immunologic insensitiveness of the skin in the young. This possibility has been suggested by several patients in whom stormy symptoms, unaccompanied by a positive cutaneous reaction, developed after the first ingestion of milk or egg. Later on, however, usually toward the end of the first year, positive reactions could be elicited.

Discussion, in any great detail, of the points brought up by Dr. Talbot would be almost too lengthy for this hour; but there is considerable experimental evidence which offers a fascinating field for speculation.

It is unquestionably true that babies fed a new food rich in protein show definite immunologic evidence of the absorption of the food from the gastrointestinal tract, such as the presence of precipitins to the specific proteins in the blood, the presence of a transitory cutaneous reaction, and occasionally the appearance in the blood serum of an antibody which is capable of sensitizing an animal passively to the protein which was given.

Practically all children pass through this experience. One could speculate as to the possibility that it is a natural immunologic process and that certain persons, who have a hereditary tendency, become permanently sensitized while others do not.

Dr. Franklin Paul Gengenbach, Denver: It is a well known observation that many children who are sensitive to milk may tolerate it better when it has been boiled a long time or has the form of evaporated milk or lactalbumin-free milk. Has Dr. Hill had an opportunity to observe the same difference between fresh goat's milk and canned evaporated goat's milk?

Dr. Lewis Webb Hill, Boston: I can't answer Dr. Gengenbach's question from personal observation, but evaporated goat's milk should theoretically be better than fresh milk for sensitive patients.

I want to read a classic piece of descriptive medical writing, from the most complete and most carefully written article on severe milk idiosyncrasy. It was prepared by Dr. Park in 1920, with his usual care and meticulous accuracy; I recommend it for those who wish to understand the nature of milk idiosyncrasy of severe degree. This is what happened to his patient after ingestion of 3 drops of a condensed milk mixture:

"He vomited violently, yellowish green bile, no milk; turned pale, began to take short, panting breaths; his eyes rolled upward and lips turned blue. He vomited again and lay exhausted; turning again deathly white, he vomited once more and panted for breath. He was too far gone to cry. His lips again turned blue. The attack lasted forty-five minutes. His mother thought death was imminent."

HERPETIC STOMATITIS: AN ENANTHEM. DR. KATHARINE DODD, DR. JOHN BUDDINGH (by invitation) and DR. LELAND JOHNSTON (by invitation), Nashville, Tenn.

Acute diseases of the mouth are common in childhood. Of the diseases in which lesions occur on the buccal mucosa and gums alone, only for thrush is the cause known. Twenty-eight cases of a type of gingivostomatitis which is common in infancy and childhood were investigated experimentally by inoculation of material from the lesions into the cornea of the rabbit. In every instance but 1 there developed vesicular keratoconjunctivitis typical of that produced by the herpes virus. The lesions could be reproduced in a second rabbit by transfer of material from the cornea of the infected rabbit. When the corneal lesions were examined microscopically, acidophilic intranuclear inclusions typical of herpes simplex were observed. Immunity to a known strain of herpes simplex was demonstrated in 7 of 8 rabbits which survived the primary infection. Six dissimilar lesions of the mouth, clinically unlike herpes, did not yield a virus when swabbings were inoculated in the rabbits' corneas. The disease is acute infectious gingivostomatitis, sometimes laryngitis, for which we have shown that the virus of herpes simplex is the cause. It is transmitted from child to child or acquired from adults with labial herpes. It is a primary disease with a characteristic enanthem and disease picture. One attack confers immunity against recurrence of the disease and perhaps relative immunity against infection with the virus of herpes simplex.

TREATMENT OF ACUTE STOMATITIS. DR. CHARLES HENDEE SMITH, New York.

The classification and nomenclature of stomatitis are much confused. Over thirty terms are in use, many of them referring to the same disease, and different writers use the same term for different varieties. There are two common conditions.

The first is the ordinary canker sore, a vesicle becoming an ulcer, single or multiple, causing no constitutional symptoms and at times accompanied by labial herpes. Some persons have recurrences throughout life from the factors which cause herpes, e. g., indigestion, fever and menstruation. This form is commonly called herpetic stomatitis.

The second is "trench mouth," an acute disease seen mostly in early childhood but also up to adult life, sporadically or in epidemics. It begins with fever, aches and pains and prostration. The patient feels really ill for several days. After a day or two inflammatory lesions develop in the mouth, with swelling and redness, then ulceration, great pain on eating and enlargement and tenderness of the lymph nodes. At this stage the patient is the picture of misery. The gums are often the main site, with a few ulcers on the tongue, the cheeks and the lips. Sometimes the discrete ulcers dominate the picture, and the gingivitis is minimal ("aphthous stomatitis," a poor term). I believe that all forms represent a single disease, gingivostomatitis. It lasts from ten days to three or four weeks. The cause is unknown, and the bacteriologic data are unsatisfactory. The condition has been attributed to the Vincent Plaut organisms, but it is probable that their presence is accidental. A virus may be responsible.

Various remedies have been used: alum, silver nitrate, copper sulfate, zinc sulfate, a solution of formaldehyde, mild protein silver, mercurochrome, iodine, ipecac, benzoin, myrrh, ascorbic acid, potassium permanganate, hydrogen peroxide, sodium perborate, methylrosaniline (gentian violet) and many others. The last two are in style at present, but I have seen no benefit from them or from any of the others. Potassium chlorate, formerly supposed to be a specific remedy, is probably useless and not without danger. Arsenic solutions applied locally and arsphenamine given intravenously have been tried, but the results are unsatisfactory. There is no excuse for using a dangerous remedy when there is no real evidence of its value.

For years dentists have used chromium trioxide (chromic acid) locally. Many papers and the best textbooks in dental literature confirm its value. I have found no mention of it in medical literature except a blanket condemnation of all "caustics." About fifteen years ago this remedy was tried on the advice of S. W. Van Saun, D.D.S. The results were so good that it has been used as a routine.

The technic of the use of chromium trioxide is important, and no results may be expected unless it is properly applied. The mouth is cleaned with any wash (such as hydrogen peroxide, sodium perborate or compound solution of sodium borate), and all necrotic material is gently wiped away. The ulcers are then thoroughly dried and touched with a 7 per cent aqueous solution of chromium trioxide on a cotton swab. The solution is worked between the teeth and gums. One third of the dental arch is treated at a time. This therapy is repeated twice a day for two or three days then once a day as long as there are ulcers. Mouth washes may be used between treatments if the patient is old enough. There is no great advantage in any particular wash, and any that the child will use will do. Compound solution of sodium borate gives the most comfort.

The treatment causes no pain and gives immediate relief, and the patient can eat with little discomfort at any time within several hours after treatment. This alone would justify its use. The whole mouth improves in twenty-four to thirty-six hours; the lesions retrogress, although complete healing of so severe an ulceration cannot be expected for several days. There is superficial coagulation, mostly of the necrotic surface of the ulcers, but there is no deep cauterization, atrophy of the gums or other bad effect.

The diet should contain nothing sour, salty, spicy, too sweet or too hot. Cereal gruels, soft milk toast and milk soups are taken best. Stomatitis is a debilitating disease and needs rest in bed and careful nursing, not only in the febrile stage but until the patient is able to eat freely and has regained some of the lost weight.

DISCUSSION

DR. FRANKLIN PAUL GENGENBACH, Denver: I add my testimony to the efficacy of the treatment suggested by Dr. Smith. Like him, I learned it from the dentist associated with my co-workers and me. We use a 5 per cent solution of chromium trioxide, but after several minutes we apply hydrogen peroxide; it certainly gives better relief than anything else we have ever tried. It not only seems to make the patients more comfortable, but it shortens the duration of the disease.

DR. JOSEPH BRENNEMANN, Chicago: It is always disquieting when one has for many years been satisfied with a certain interpretation to find that some one has come along with an entirely different theory of origin. I have observed cases of these conditions for many years. I have always thought they they were associated with infections of the throat or of the upper respiratory tract. Many years ago I stated that two conditions that were not frequently enough emphasized in connection with throat infections were stomatitis and conjunctivitis. Dr. Dodd's presenation is extremely interesting because of its scientific flavor, but I still have reservations in the matter.

With a disease which is self limiting and which in New York lasts thirteen days, in San Francisco eleven days and in Chicago seven to ten days, one may at least question whether it is better to disturb a baby with unpleasant treatment, no matter of what type, than to leave it alone. That applies also to the use of chromium trioxide, even if the child feels better after the application. I emphasize one point in treatment, and that is that the child should be given food which is cold, not warm, and certainly not hot, because cold is grateful and heat decidedly not.

There has recently been an elaborate scientific demonstration that these conditions are due to the fusospirochetal complex plus a symbiotic relation with at least two other organisms. If the theory just presented is fully confirmed the former theory of origin will be supplanted, as I have always felt it would be.

DR. WILLIAM L. BRADFORD, Rochester, N. Y.: Does Dr. Dodd consider aphthous stomatitis to have a cause different from that of Vincent's stomatitis? I have often found it difficult to differentiate the two conditions clinically and have obtained little help from descriptions given in the accepted textbooks. I believe that Fischl [2] refers to the fact that aphthous stomatitis and the Vincent's type of ulcerative stomatitis produce lesions on the gums, while the herpetic types does not.

If herpetic stomatitis and herpes labialis are due to the same virus, it is of exceptional interest that the former infection should result in immunity, since it is known that apparently little immunity results from the occurrence of fever blisters.

The repeated obtaining of herpes virus from the lesion strongly suggests that it is related to the lesion, but can a virus-bacterium relationship exist in this disease?

DR. ARTHUR F. ABT, Chicago: I corroborate Dr. Smith's use of chromium trioxide. I also learned this treatment from my personal dentist. I agree with Dr. Brennemann that the disease lasts about a week in Chicago and that chromium trioxide has no effect on its duration. However, this drug has a pleasing effect on a sore gum, and I have noticed that the infants and children for whom I have used it sleep better and eat better after treatment.

DR. ALFRED HAND, Philadelphia: I should like to ask Dr. Smith a rather personal question, based on his statement that he is subject to attacks of "canker sores." Has he ever had the thought that it might be a type of food anaphylaxis?

Whenever I see a case of aphthous stomatitis, I find the tongue coated and I treat the stomach. It does not make much difference what I use in the mouth; the patient recovers. Dr. Smith emphasized the herpetic nature of aphthous stomatitis, which suggests the relation between herpetic stomatitis and herpes facialis. I know of 2 cases of the latter in which the condition was directly dependent on the eating of shellfish. Phlyctenular conjunctivitis is also a form of herpes. In an interesting article published a few years ago in an issue of *The Journal of the American Medical Association* an ophthalmologist stated that cataract is due to food anaphylaxis. In the discussion Dr. Ulysses Moore of Portland, Ore., described his experience with phlyctenular conjunctivitis, which had incapacitated him for about 40 per cent of his time from the age of 25 to the age of 40 years. The ophthalmologists were thinking of enucleating his right eye, when finally he came in contact with a modern pediatrician, who suggested that the condition was a type of food anaphylaxis. Dr. Moore was tested; since then he had had only one attack, a light one deliberately produced by injestion of a small piece of beefsteak. He said he would never touch another bit of steak or tunafish.

DR. KATHARINE DODD, Nashville, Tenn.: All of the animal work was done by Dr. Buddingh and Dr. Johnston, of Dr. Goodpasture's department. Dr. Goodpasture oversaw all the work we did; he feels that there is no doubt that the stomatitis of infants is caused by the herpetic virus.

For many reasons there is a great deal of confusion about herpetic stomatitis. Inflammation of the gums in adults is not usually due to this disease. I am talking about an acute contagious disease which is extremely common in infants. It is so nearly universal in infancy that it may seem less contagious than it is. If there is a large family of children, most of them probably already have had the disease and therefore do not catch it from the youngest member. Herpetic stomatitis occurs earlier in life than most of the other contagious diseases.

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2. Fischl, R.: The Diseases of the Oral Cavity, in Pfaundler, M., and Schlossmann, A.: The Diseases of Children: A Work for the Practicing Physician, translated and edited by M. G. Peterman, Philadelphia, J. B. Lippincott Company, 1935, vol. 4, p. 1.

Herpetic stomatitis and herpes labialis are caused by the same virus, but there are many things not known about the herpes virus. It is known that after a primary infection the herpes virus remains in the body in many instances, perhaps in a nerve ganglion, and appears later as herpes labialis, during menstruation or with an infection or perhaps when the patient eats certain foods. This is a reappearance of the disease from the inside rather than infection from the outside. It is also true that reactions of adults to certain diseases are very different from those of children. It may be that small children react in a more serious manner to the herpes virus than adults and that whereas children almost always have the primary infection in their mouths the mucous membrane of the adult may have become relatively immune, so that he has the primary infection on the skin.

Anything that can make these children more comfortable is worth trying, but we have had the same experience as Dr. Brenneman; anything we do seems to make the mouth more rather than less sore. Only children with dirty teeth and ill kept mouths are apt to get secondary infection. Treatment may sometimes help to prevent this.

Dr. Black and others have shown that it is impossible to implicate any specific bacterium by showing that it is constantly associated with herpetic stomatitis. It therefore seems unlikely that both herpetic virus and a specific bacterium are necessary to produce the disease.

DR. CHARLES HENDEE SMITH, New York: Dr. Dodd's statements about age are perfectly correct. Stomatitis is seen most often in the first three years. But it does occur in later childhood and in adult life, and I believe with a good many writers that the trench mouth of armies is this same disease in adults.

"Aphthous" stomatitis is a most unsettled term. Dr. Hand uses it in a different sense from that of Dr. Dodd. Stedman's dictionary says that aphthous stomatitis is thrush; I wish we could throw the word out. Aphthae are merely ulcers, and since the word is never used in any other connection it could be spared. I think Black's suggested term "gingivostomatitis" is the best.

The theory of Vincent's organisms was abandoned years ago. These organisms are so inconstantly present in many of these cases that they are obviously casual inhabitants.

I believe that sometimes gingivostomatitis affects chiefly the gums and that sometimes solitary ulcers predominate. The physician who thinks about the solitary ulcers calls the disease aphthous stomatitis, but the gums are always involved. When there are a few solitary ulcers and much gingival involvement the condition is called gingivitis.

This is a definite disease entity. But I wish Dr. Dodd would not call it herpetic yet. The term adds to the confusion, because many textbooks have used it to indicate the common canker sore. To transfer a term from common usage is confusing.

Dr. Brennemann has not studied stomatitis longer than I have. I have always been especially sorry for these children, for I know of no more uncomfortable disease. I have tried to help them instead of letting them lie in bed in misery for ten days or even for two or three weeks just because the disease subsides in time. With other diseases physicians relieve pain. Even though they are self limited, one treats such diseases as typhoid fever and pneumonia. Why let any child suffer unnecessarily?

How is it known that chromium trioxide gives relief? Because the testimony of older children and of adults who have this treatment is so convincing. Also, as Dr. Abt says, the young babies eat better and sleep better. After all, relief of suffering is one of the chief objects of treatment.

TWO CASES OF COMPLETE RECOVERY FROM SPORADIC CRETINISM. DR. ALFRED HAND, Philadelphia.

Recovery from sporadic cretinism is sufficiently rare to justify presentation of 2 cases from private practice.

CASE 1.—A girl when first seen, at 19½ months of age, had the classic symptoms: depression of the bridge of the nose, constant protrusion of a large tongue, a heavy expression, a prominent abdomen, lordosis, stocky legs, inability to walk alone and no beginnings of speech. The first tooth erupted at 18 months; two teeth were present on admission; the infant did not sit up alone until 9½ months old. Administration of desiccated thyroid in a total daily dose of ¾ grain (0.05 Gm.) produced a visible effect on the tongue in four days; the dose was then raised to 1½ grains (0.09 Gm.) daily, with great improvement. After four months the child had thirteen teeth and was lively, playing, running, speaking single words, perspiring and sometimes crying. Development was normal through childhood and adolescence; when last seen, at 18 years of age, she was 5 feet and 5¼ inches (166.7 cm.) tall and weighed 140 pounds (63.5 Kg.). She was well educated and able to speak English, German, French and Spanish. She married two years later.

CASE 2.—An infant girl under observation developed normally from the second to the twelfth month. She was seen once at the end of the second year; at this time she was rachitic and pale; there were eight teeth; signs of cretinism were not noted. At the next visit, nine months later, she looked distinctly cretinoid: The tongue was large and protruded; she had a heavy expression, lordosis and stocky legs, and the speech was limited to single words. Three fourths of a grain of desiccated thyroid was given daily for three weeks, with improvement; medication was omitted for one week, continued at the level of 1½ grains daily for three months and neglected for one month. Then for seven years thyroid treatment was irregularly intermittent; the child would be seen with various acute infections, and after recovery thyroid would be prescribed but would not be given persistently. Yet, she was able to go to school, doing well in some studies but poorly in arithmetic (Kerley) and not playing animatedly. At 9½ years all the deciduous teeth were still present, and the 6 year molars were not erupted; the height and weight were in the range of standard figures for 5 years, being 3 feet and 6¾ inches (108.7 cm) and 44 pounds (20 Kg.). Administration of a mixed glandular preparation was then started, the maker's formula stating "Thyroid extract, gr. 1/32, extracts of thymus, spleen, suprarenal, pancreas, lymphatics, brain, with pepsin, salivary and excipients," the amounts in the 3 grain (0.19 Gm.) tablet not being stated. Improvement in the general condition and in the behavior was noticed in three weeks, so the treatment was continued persistently and faithfully. Steady growth followed, and in five years, at 15 years of age, the patient had overtaken her age group, being 4 feet and 9¾ inches (146.7 cm.) tall, weighing 78½ pounds (35.6 Kg.) and having a perfect set of permanent teeth free from caries. She graduated from high school a year ago, and now, at 22 years of age, she weighs 105 pounds (47.6 Kg.) and is 5 feet and 3¼ inches (161.9 cm.) tall, 1 inch (2.54 cm.) taller than her mother.

The cause of the striking improvement in case 2 is not perfectly clear. At first it was attributed to one or more of the ingredients in the pluriglandular preparation; but with the somewhat recently developed idea that if more thyroid substance is taken than the patient needs harm may be done, there is the possibility that the original dose of ¾ grain daily may have been too large. The later minute dose of 3/32 grain (0.00605 Gm.) daily may have been enough to make good the deficiency of the patient's thyroid gland and perhaps to act as a hormone; the succeeding doses occasionally reached a little over ⅛ grain (0.01295 Gm.) daily, the average range being probably from 1/12 to ⅛ grain (0.0054 to 0.0081 Gm.).

DISCUSSION

DR. CHARLES G. KERLEY, New York: Subthyroidism has always interested me greatly. I have 8 patients whom I look on as normal, 7 of them young women. The oldest, now aged 40 years, has been under my observation since she was 6 weeks old. None is married. The best proof of normalness is that the subthyroidism is known only to the immediate families.

The eighth patient is a boy. At the age of 7 weeks he was a typical textbook cretin. At the age of 5 years he presented every appearance of a normal child as regards height, weight and intelligence. At the age of 9 years his school report card showed him in the proper grade for his age, with a perfect record in reading, writing, arithmetic and composition, and a satisfactory record in all other studies. He has been under constant thyroid therapy. At present he is getting 3 grains (0.19 Gm.) of thyroid a day. It has always been given to the point of physiologic effect.

EFFECT OF VARIOUS FEEDINGS ON LOSS AND GAIN OF WEIGHT DURING THE NEWBORN PERIOD. DR. HEYWORTH N. SANFORD, Chicago.

In a nine year study of 4,622 newborn infants during the newborn period who were given various forms of complementary feedings or breast milk alone, the following conclusions can be drawn.

Regardless of whether a complement is used, approximately 33 per cent, or one third, of newborn infants will lose between 5 and 8 per cent of the birth weight. One may assume that this is about the average loss of weight of the average newborn baby. This loss may be decreased by the feeding of a complement to the breast milk and is to some extent inversely proportional to the caloric value of the complement. The higher the caloric value of the complement the less the loss of birth weight. With ordinary complementary feedings, even including 5 per cent dextrose, about half of the newborn infants will lose only 5 per cent or less of the birth weight. With complementary feedings of a high caloric value the proportion of babies may be increased to two thirds. Conversely, it is exceptional for an infant given any form of complementary feeding to lose as much as 10 per cent or more of its birth weight, but of infants not given any complementary feeding, one must expect that with six nursings of breast milk in twenty-four hours 18 per cent, or approximately one sixth, will lose 10 per cent or more of the birth weight. When only five nursings are given in a twenty-four hour period, one must expect 25 per cent, or one fourth, of the children to lose 10 per cent or more of the birth weight.

About half of the newborn infants given a complementary feeding will have regained the birth weight within ten days from birth. The proportion is influenced by the caloric content of the complementary feeding given. The higher its caloric value, the more likely it is that the fraction of babies regaining weight will exceed one half, and the lower the caloric value, the less likely the fraction is to reach it. If newborn infants are given no complementary feedings but are nursed six times each twenty-four hours, one quarter will have returned to the birth weight at the age of 10 days, and if only five breast feedings are given only one seventh will return to the birth weight. However, this is due to the greater initial loss; actually the gain of weight is faster than in those given complementary feedings.

DISCUSSION

DR. BÉLA SCHICK, New York: About twenty years ago I made a similar study on complementary feeding of newborn children. I studied first the problem of whether it would be possible to avoid the physiologic loss of weight in the newborn period by forced feeding, but I dropped forced feeding because I found it was not necessary.

The second question was, Should complementary feeding be done at all? At first I studied the different forms of complementary feeding, just as Dr. Sanford did, and I found certain facts which would be too complicated to discuss here.

The main issue, as I found, concerned weak children, children with low weight and, of course, premature infants. They have to be watched carefully and must not be left alone, because acetone appears quickly. We made studies of acetone appearing in the urine; acetone was found forty to fifty-five hours after birth.

If one is sensitive to the odor of acetone one can go around the newborn station and pick out all the children who are starving; starvation in the newborn period should be avoided.

It is interesting to see how quickly the acetonemia can be avoided by additional feeding of some carbohydrate. It is not necessary, of course, to give the full amount of feeding or the full amount of complementary feeding. Such children did better with additional feeding. I recommended that only children of weights below 2,000 Gm. should be watched and eventually should get complementary feeding, whereas the stronger children should be left alone. I cannot imagine that it is advantageous for newborn children of low weight to starve.

I was also interested in the question as to whether the newborn child is like a plant, which can grow for a short time with water only, or whether he needs real food. A newborn child looks somewhat better with water alone, but it is much better if he gets at least carbohydrates in addition.

Dr. Charles Hendee Smith, New York: Dr. Schick's last remarks ought to be emphasized. Newborn infants need at least carbohydrates and water. They do not all need formula feeding until the breast has had a fair trial. As I showed a few years ago, over 90 per cent of the babies born in Bellevue Hospital reach the birth weight by the tenth day without complementary or supplementary feedings. No formula is given until it is proved that they are not going to get breast feedings.

Another objection to prelacteal feeding is the possibility of establishing an allergy with a few doses of milk. Furthermore, all three of Dr. Lyon's charts of diarrhea of the newborn showed that the infants gained 10 ounces (283 Gm.) or more in the first ten days. If one grants them a physiologic loss of at least 4 ounces (113 Gm.), it is evident that they had an amount of food which caused a gain of almost a pound (450 Gm.) in the first ten days. This is an unphysiologic, dangerous rate of gain. I do not doubt that the children had some infection besides, but the overfeeding may well have paved a way for it. Dr. Lyon says he was not responsible for the early feeding. I believe it is behind these early diarrheas in many cases. The relation of this factor to so-called epidemic diarrhea of the newborn has not been properly studied.

Dr. Heyworth N. Sanford, Chicago: I tried not to let my personal opinions about feeding the newborn enter into this discussion. The results of this study are shown, and one can use one's own judgment. Whatever the choice may be in feeding the newborn there are two problems. First, if the baby is to gain rapidly in weight, obviously the feeding should be made of as high a caloric value as the child's digestive apparatus can stand. Second, if the infant is to be breast fed, it should be noted that complementary feeding of the higher caloric values will reduce the number of babies that will be breast fed or at least of those who obtain sufficient breast milk.

In regard to what Dr. Schick said about the factors that influenced his study, I agree; they probably include not only weight but sex and season. I did not wish to discuss this because it will be entered into in a paper which I am giving next month at the meeting of the American Medical Association.

In regard to feeding a small baby, obviously one cannot allow such a child to lose too much weight. It is ridiculous to let the weight approach that of a premature infant while one is waiting for sufficient breast milk from the mother. One need not fear that the small baby will have difficulty within seventy-two hours from birth because as a rule about three days elapse before acetone is actually found in the urine of a newborn child. So two days may be allowed for the mother's breasts to begin secretion; but I emphasize again that I do not believe in permitting these small babies to wait too long before artificial feeding is started. These studies show that 5 per cent of the mothers will have no breast milk and that an additional 9 per cent will have hardly enough to make nursing worth while. Thus 14 per cent of the infants will definitely have to be given complementary feeding, and approximately 30 per cent more will have to be given some addition to the breast milk.

Final Session

Saturday Morning, April 29

CONCENTRATED HUMAN BLOOD SERUM AS A DIURETIC IN NEPHROSIS: FURTHER OBSERVATIONS. DR. C. ANDERSON ALDRICH and DR. H. H. BOYLE (by invitation), Chicago.

This paper reports the results of treating with concentrated human blood serum 7 patients who had pure nephrosis. These results are studied from the standpoint of diuretic effect and from that of ultimate prognosis.

In these patients diuresis was uniformly produced when the serum was administered in adequate doses, provided no acute infection complicated the picture. The elimination of fluid was always complete, although not always permanent.

When these cases are tabulated with those reported last year by Aldrich, Stokes, Killingsworth and McGuinness, it can be seen that the ultimate prognosis was much better for the patients treated during the first six weeks of the disease. This suggests that concentrated serum should be tried early rather than used as a last resort method.

Experience with many patients who had hematuric types of nephritis has been disappointing, none having responded in a satisfactory manner.

DISCUSSION

DR. WILLIAM THALHIMER, New York: I shall present two simple inexpensive methods of concentrating serum under sterile conditions and a simple method of drying serum in the frozen state. These methods can be used in any well equipped laboratory, obviating the need of expensive apparatus.

Commercial cellophane sausage casing about 2½ inches (6.3 cm.) in diameter is made up with a special glass funnel at one end and the other end tied securely with heavy twine. This is sterilized in an autoclave at 30 pounds' pressure for fifteen minutes and then weighed empty on a spring balance. The casing is then filled with about 1,500 cc. of sterile serum and again weighed to determine the net weight of the serum. The filled casing is suspended from its tied end in front of an electric fan either in a room of the usual temperature or in a mechanical refrigerator. The moisture evaporates rapidly, and the weight of the serum is reduced to one third in thirty-six to forty-eight hours.

The concentrated serum is passed first through a sterile paper pulp filter and next through a Berkefeld filter and then is vialed and tested for sterility. During storage in the refrigerator at 5 C. the serum may become slightly cloudy, but this is caused apparently by separation of fatty materials, and the cloudiness clears up when the serum is warmed to body temperature.

This serum has been administered intravenously in amounts up to 150 cc. to between 20 and 30 children and adults without causing reactions in a single case.

It seemed that a method might be of value which would concentrate the protein fractions of the serum and simultaneously remove some of the salts and the nonprotein nitrogenous materials. This has been accomplished by immersing the sausage casings filled with serum in colorless, commercial corn syrup. The water diffuses out rapidly and with it a considerable amount of the salts and nonprotein nitrogenous materials. Thus the protein has been concentrated three times, and the salts and nonprotein nitrogenous substances have been reduced to one third.

This method also has been used in concentrating ascites fluid; in 1 sample the protein was concentrated seven times, and the salts were reduced to one seventh of the calculated amount.

With the corn syrup method from 6 to 8 per cent dextrose enters the serum, either with or without a slight trace of dextrin.

It is perhaps an advantage in some instances to add the dextrose to the serum, as it may act as an additional aid to diuresis.

It was important to find out if any danger could be caused by the intravenous injection of even a small amount of dextrin. Dr. Francis Murphy, of Milwaukee, who has been interested in the therapeutic value of the intravenous injection of a 50 per cent solution of sucrose, made careful tests to determine whether dextrin injected intravenously has any deleterious effect. A 50 per cent sterile solution of corn syrup (containing about 20 per cent dextrin) injected intravenously into rabbits was found to have no pyrogenic or other harmful effect. Dr. Murphy first injected small amounts of this serum intravenously into patients with increased intracranial pressure, gradually increasing the dose from day to day until large amounts were given at one injection. There was no deleterious action whatsoever, but the injection of a 50 per cent solution of corn syrup did not reduce the intracranial pressure as much as the 50 per cent solution of sucrose.

It was next thought that serum might dry in a sterile cellophane bag while in the frozen state, just as wet clothes hung on the line out of doors in winter, when the temperature is below freezing, will lose moisture and dry.

Small and large cellophane bags filled with serum were placed in a refrigerator room with a temperature below freezing, some of them in a current of air from an electric fan. The serum remained frozen, drying completely after a longer or shorter period, became white, had the same porous consistency as serum dried by the lyophil process and redissolved just as rapidly. Small bags of serum were also kept in the refrigerator room in a vacuum desiccator under a high vacuum, and the drying process proceeded much more rapidly. At atmospheric pressure a small sausage casing containing 10 cc. of serum will dry from the frozen state in two or three weeks. In the vacuum desiccator this will occur in three or four days. Larger amounts take considerably longer.

This method should prove of value for drying and preserving valuable serums for research purposes. Also it may be useful in drying large amounts of serum for routine use.

Clinical investigation is proceeding with the use of concentrated serum prepared by either the air or the corn syrup technic for patients with lipoid nephrosis, shock, pulmonary edema and other conditions.

The use of concentrated ascites fluid is being tried out under similar conditions.

REACTION OF THE EDEMATOUS PATIENT TO TRANSFUSION WITH SERUM OR WITH ACACIA. DR. J. D. LYTTLE, DR. E. GOETTSCH (by invitation), and DR. A. A. WEECH, New York.

Observations were made during the treatment of edema in 10 children with nephrosis and in 4 dogs with nutritional edema. The children received intravenous injections of serum or solution of acacia; the dogs were given concentrated serum albumin. Diuresis was initiated in 1 of 6 children who received serum, in 2 of 4 children treated with acacia and in all of the 4 dogs. Analyses of serum did not disclose significant differences in albumin concentration or in calculated colloid osmotic pressure between cases in which diuresis occurred and those in which it did not. Change in albumin concentration was usually slight and always transient. In 1 nephrotic child a large part of the injected serum was soon lost in the urine. Other observations, which include hematocrit readings before and after the injections and direct measurements of plasma volume, indicated that injections of serum or solution of acacia always result in an increase in the volume of the blood. The question was raised as to whether the increased blood volume is not itself the factor inciting to diuresis. In 1 dog diuresis was produced on two occasions, once by the injection of serum albumin and again by the transfusion of red cells washed free of plasma. Since both injections increased the volume of the blood, the result suggests a relation between the increase and the ensuing diuresis. It was pointed out that the possible existence of such a relationship should be recognized in the planning of therapeutic procedures.

DISCUSSION

DR. ALLAN M. BUTLER, Boston: My co-workers and I have used concentrated serum in the treatment of 8 patients with nephrosis and 1 patient with chronic glomerular nephritis. Our doses of serum have been larger than the doses used by Dr. Aldrich. In 1 case, using both concentrated and ordinary serum, we raised the total to the equivalent of 1,730 cc. of serum. Only 1 of the patients had diuresis such as that reported by Dr. Aldrich. This patient had had nephrosis for a very short time. On admission to the Deaconess Hospital the patient was found to have urinary infection and was given sulfanilamide. With this therapy there were diuresis and a loss of 8 pounds (3.6 Kg.). Before this diuresis had ceased, 100 cc. of serum was given in three days; this was followed by further diuresis and a loss of 17 pounds (7.7 Kg.), so we do not know whether in that particular case the diuresis was the result of the serum therapy or of the sulfanilamide therapy.

In the other 8 cases there was no diuresis or shift in the serum protein.

We have a patient who is of interest in illustrating the change in blood volume mentioned by Dr. Weech. We did not measure the blood volume, but this patient was having a serious collapse, such as described by Dr. Farr, except that he had real peritonitis. He was desperately ill; the extremities were cold, the pulse was weak and rapid, and the circulation obviously was bad. We felt that this was largely due to a drop in blood volume, which is often encountered in these nephrotic patients. We gave concentrated human serum, and immediately there was a most extraordinary change in the patient's appearance. The pulse improved, the rate slowed, the hands and feet became warm, and the circulation was markedly improved.

We have had 52 patients with nephrosis. Of these, 18 have died and 2 are still seriously ill, while the remaining 32 were apparently on the road to complete recovery when last heard from.

DR. IRVINE MCQUARRIE, Minneapolis: The paper presented by Dr. Weech and co-workers suggested a possible explanation for an experience that my associates and I had in a case of nephrosis. It appears to confirm his finding with regard to blood volume.

The patient referred to was given more blood over a period of four days than her total blood volume. The serum albumin was increased only slightly as a result of this procedure. Her hematocrit reading, however, was well above 60 per cent, and she had polycythemia, with more than 8,000,000 red blood cells. In general appearance the child resembled a patient with polycythemia vera, or Osler's disease.

While the value of serum proteins still ranged between 3.5 and 4.5 per cent, with reversal of the albumin-globulin ratio, diuresis suddenly developed four or five days after the height of the polycythemia had been reached, and most of the edema was lost. We could not explain this diuresis on the simple basis of colloidal osmotic pressure relationships.

Dr. Whipple has shown clearly in the case of the normal dog that serum proteins given intravenously enter into the protein metabolism in some way. It may be presumed that the proteins do not get out through the intact capillary walls but that the various cells lining the capillaries, that is, the endothelial cells, may take up the protein. I should like to know in reference to cases like those presented by Dr. Weech whether or not the total serum protein in the urine accounted for all of the protein given by the intravenous route or whether some of that lost from the blood stream was not taken into the depleted tissues to replace the basic materials from which the serum proteins are manufactured. It is conceivable that a great deal of extra protein administered under these conditions may enter into the general protein metabolism and so fail to elevate the level of serum proteins to the extent expected.

The tremendous loss of serum proteins by way of the kidneys after administration of serum indicates the need for investigation into the possibility of producing

effective antidiuresis of the serum proteins. In studies on the effect of pitressin against nephrosis, we found 1 case in which there actually appeared to be antidiuresis of serum albumin as well as of water. We expect to follow up this suggestive lead.

DR. JOHN D. LYTTLE, New York: The children who received lyophil serum had severe reactions. The temperature rose to 106 or 107 F.; they had chills, involuntary defecation and shock. The same reactions were at times observed with acacia, but as the quality of acacia improved we were able to guard against them. No reactions at all followed the injection of serum concentrated by Dr. Thalhimer.

A drop in hematocrit values shows that fluid has been drawn into the circulation, but unless there is progressive action and the kidney excretes it, diuresis does not take place. It may be that success is due to a shock reaction associated with the sudden increase in plasma volume. The mechanism and the explanation for the different results obtained are certainly not clear.

DR. L. EMMETT HOLT JR., Baltimore: I should like to call attention to a method for concentrating serum or protein solutions which may possess some advantage over that used by Dr. Thalhimer in the fact that additional sugar is kept out. Degkwitz, in Germany, has shown that a collodion membrane impregnated with copper ferrocyanide is impermeable to sugar; with dialysis in such a sac against a concentrated solution of sucrose, water goes out and sugar does not come in as it does with the ordinary collodion membrane.

DR. DANIEL C. DARROW, New Haven, Conn.: Does Dr. Weech have evidence of the nature of the protein lost after the transfusions? Specifically, do the transfusions lead to greater loss of the abnormal serum albumins which have been found in cases of nephrosis?

DR. CHARLES ANDERSON ALDRICH, Winnetka, Ill.: We have seen diuresis occur after injection of large amounts of unconcentrated solutions and after transfusions, but we have never been able to get this result nearly as regularly as with the concentrated serum. I want to thank Dr. Weech for his demonstration of the hydremic plethora, if that is what one should call the response. It always seemed to me that if there was any understandable explanation of the complete diuresis, it would be found in the idea that the blood injected acts as a sort of carrier for water, which is taken out of the tissues and carried around to the kidneys by some chemical substance in the blood.

I agree with Dr. Lyttle's idea that the cause of spontaneous diuresis is not known. Until it is, one is not going to talk intelligently on the subject. For many years I have spoken of the unknown mechanism of these renal crises; nephrosis will be finally understood when these spontaneous crises are understood.

One thing should be emphasized. There is a difference between the nephrosis which does not and the so-called nephrosis which does show red cells in the urine. This is borne out by the fact that we have never seen serum diuresis of any patient who ever showed red cells in the urine. We have rigidly excluded from this group all patients who showed any degree of hematuria. I believe this is not true in some of the other series reported.

Our results showed that these injections should not be used when there is any active infection present in the patient, when there is any blood in the urine or late in the disease. It therefore should be used as a first rather than as a last resort.

DR. A. ASHLEY WEECH, New York: Dr. McQuarrie has asked if the serum protein which is injected enters into the body metabolism. There can be little doubt that this is true; the experiments of Dr. Whipple, to which he referred, demonstrate convincingly that homologous serum protein can be metabolized when given by vein. With the patient for whom we followed the urinary excretion of protein after the injection of serum, only half of the protein which disappeared from the circulation during three days was accounted for in the urine; the remainder was probably metabolized. When injections of serum are given to

animals with nutritional edema, there is a similar loss of protein from the circulation. Such animals do not exhibit albuminuria, and one is forced to assume that the protein has been metabolized.

Dr. Darrow has asked about the nature of the protein in the urine after these injections. I believe he refers to the work of Dr. Goettsch, who by an immunologic technic demonstrated the presence of abnormal albumin and abnormal globulin in the serum of patients with nephrosis. At the present time Dr. Goettsch's findings indicate that the urinary protein in nephrosis is normal serum protein and not the abnormal fraction which exists in the circulation. Under the circumstances the immunologic method could not be used to identify the extra protein which appears in the urine after injections of serum.

EXPERIMENTAL STUDIES CONCERNING THE PATHOLOGY OF INSULIN CONVULSIONS. DR. IRVINE MCQUARRIE and DR. MILDRED R. ZIEGLER (by invitation), Minneapolis.

The investigation reported was undertaken primarily to determine whether or not there is any significant relation between decrease in the potassium or the inorganic phosphate of the serum and the occurrence of convulsions after administration of insulin in convulsive doses. A variety of experimental conditions were employed. The effects of maintaining normal levels of serum potassium and of inorganic phosphorus by administering salts of these elements during periods of insulin hypoglycemia were determined. In addition numerous experiments were carried out to determine the effects of breathing atmospheres varying in oxygen (O_2), carbon dioxide and nitrogen (N_2) content on the occurrence of insulin convulsions. A number of studies were made both before and after adrenalectomy. Only healthy young dogs were used in all experiments. Satisfactory standardization of such factors as diet and individual response to insulin was carried out on each animal during a preliminary control period.

The results may be summarized briefly as follows: In 86 experiments (45 dogs) on the effects of insulin alone, it was observed that convulsions tended to occur at or near the low point in the blood dextrose curve. Although the serum potassium and inorganic phosphate were also regularly decreased after injections of insulin, the occurrence of convulsions bore no constant relation to the concentration of these electrolytes. Maintenance of the potassium or phosphate levels by continuous administration of salts containing these substances did not prevent or delay the onset of insulin convulsions.

Breathing atmospheres containing between 5 and 9 per cent oxygen caused marked hyperglycemia in normal fasting dogs but was followed by fairly marked hypoglycemia in the same animals after bilateral adrenalectomy. Contrary to our expectation on the basis of the current anoxic theory insulin convulsions, anoxic anoxia of this type was found to prevent or greatly delay the onset of insulin convulsions in both normal and adrenalectomized animals instead of increasing the convulsive tendency. This was true even when the degree of hypoglycemia exceeded that associated with convulsions during the insulin control period. Breathing 15 per cent carbon dioxide had a similar effect. High oxygen atmospheres had no special effect. It was concluded from the latter studies that neither anoxia nor hypoglycemia alone accounts for insulin convulsions.

EXPERIMENTAL STUDY OF CEREBRAL CHANGES IN PROLONGED HYPOGLYCEMIA. DR. HERMAN YANNET, New Haven, Conn.

Cats were used as the experimental animals. The effect of prolonged hypoglycemia on the brain was studied by histologic and chemical means. The dose of unmodified insulin employed varied from 3 to 20 units per kilogram of body weight; it was injected subcutaneously after a twenty-four hour fast. The animals were divided into four groups. Group 1, consisting of 20 animals, served as controls. Group 2, consisting of 15 animals, were killed and examined from three

to five hours after the injection of insulin. Groups 3 and 4, consisting of 22 animals, received from 10 to 20 units of insulin per kilogram and were allowed to recover spontaneously after prolonged hypoglycemia. These animals were examined twenty-four hours after the injection of insulin. Group 3, consisting of 12 animals, showed no clinical signs of injury to the central nervous system when examined. Group 4, consisting of 10 animals, showed outspoken clinical evidence of extensive damage to the brain. The symptoms and signs presented by these animals may best be described as those of decerebrate rigidity. The following chemical changes could be demonstrated in the brains of the animals in the different groups:

In group 2 there was a significant decrease in the sodium and the chloride content with no change in total water, nonlipoid nitrogen and potassium. This change was interpreted as signifying a shift of water from the extracellular to the intracellular space, leading to cellular hydration.

The animals in group 3, which showed no clinical evidence of cerebral damage after prolonged hypoglycemia, showed neither chemical nor histologic evidence of changes in the brain.

In group 4, which showed clinical evidence of widespread injury of the brain, the following chemical changes could be demonstrated: There were an increase in the sodium and the chloride content, a marked decrease in the potassium content and no significant changes in the total water and nitrogen. These findings were interpreted as indicating a marked shrinking in the brain cells due to a shift of water from the cells to the extracellular spaces as well as a loss of cellular potassium. Evidence was also presented suggesting a shift of sodium into the cell. It was felt that these were the changes to be expected in tissue undergoing dissolution. The histologic examination confirmed the chemical findings in demonstrating marked changes in the ganglion cells of the nature of cellular condensation and degeneration.

Evidence showed that the changes in the brain following prolonged insulin hypoglycemia were not causally related to (1) convulsions, (2) cerebral anoxemia, (3) changes in blood pressure or (4) hypoglycemia per se. The available evidence suggested that insulin, by direct action on the cerebral cells, stimulates certain reactions which, in the presence of hypoglycemia, are incompatible with normal cellular metabolism and thus lead to cellular injury or death.

COMPARATIVE STUDIES ON THE USE OF STANDARDIZED PROTAMINE ZINC AND CRYSTALLINE INSULIN. DR. FRANCIS SCOTT SMYTH, and DR. MARY B. OLNEY (by invitation), San Francisco.

The program for handling a clinic for diabetic children was evolved from experience accumulated since 1925. In addition to the supervision of the diet and physical well-being, the check-up allows for information on the fluctuations of blood sugar during a normal day's activity. Evidence is presented which indicates that protamine zinc insulin with standard insulin given in the same syringe results in a more satisfactory control than is possible when more numerous injections of standard insulin are given or when protamine zinc insulin is given alone.

DISCUSSION

DR. HERMAN YANNET, New Haven, Conn.: I have one point to make that I did not have time to present. I may have given the impression that hypoglycemia itself is of no importance in the production of the damage to the brain which follows the injection of large doses of insulin. That this is not the case will be seen from the following type of experiment. If after the injection of a large dose of insulin (25 units per kilogram of body weight) the blood sugar is maintained at approximately the normal level by means of an infusion of dextrose, the animal will make an uneventful recovery and will show no evidence of cerebral injury. Thus, although there is evidence that insulin has a direct action on the brain, it is only in the presence of hypoglycemia that this action may lead to cellular damage.

HEPATIC INJURY ON A NUTRITIONAL BASIS IN RATS. DR. PAUL GYÖRGY, Cleveland.

Research on vitamin B_6 has been decidedly hampered by the fact that the ration originally used for experimental production of acrodynia in rats as a B_6 deficiency disease was, as can be seen in retrospect, incomplete in many directions. This diet consisted of casein, cane sugar, melted butterfat, salt mixture, cod liver oil, vitamin B_1 and riboflavin. Of course when this diet was used vitamin B_6 deficiency was the dominant disease, while all other possible deficiency manifestations were relegated to a latent position. Addition of purified B_6 concentrates was then followed by cure of the acrodynia-like condition, with or without the further complication of a newly manifested deficiency disease. During the course of our investigations on about 2,000 rats my associates and I have observed two diseases of this kind: hepatic injury and panmyelophthisis with hemorrhagic manifestations.

Forty-eight rats with distinctly pathologic changes in the liver were observed in the period from September 1937 to February 1939.

Occurrence of injury to the liver on a nutritional basis should be of great interest to the clinician. In this connection it is sufficient to call attention to toxic hepatitis of obscure cause and to cirrhosis of the liver, the latter particularly as it occurs in alcohol addicts. In the light of our experimental findings, one could assume that cirrhosis of the liver in man is not, or not only, of toxic origin but perhaps bears rather the character of a deficiency disease.

Hepatic injury in the rats which were kept on a diet containing not all the members of the vitamin B_2 complex was first diagnosed on gross examination by the spotty appearance of the liver, which was yellow and hemorrhagic. Histologic examination of these alterations, made by Dr. Harry Goldblatt, revealed extensive injury, which appeared in three different consecutive changes. These were (1) central necrosis in all lobes or in only a single lobe with severe fatty infiltration; (2) capillary hemorrhages due to rupture of the necrotic capillaries in and around the necrotic parenchymatous foci, and (3) a tendency toward healing, in the form of connective tissue proliferation which led to precirrhotic lesions.

As to the origin of this kind of injury to the liver, it is safe at the present time only to state that the manifestations must be partly, at least, of nutritional origin. Bacteriologic examination furnished no evidence that the lesions were infectious; however, an infection superimposed on the specific nutritional basis cannot definitely be ruled out at this time. Similar pathologic lesions have not been recorded in the literature dealing with vitamin problems. Our studies show that this type of hepatic injury can be prevented by administration of yeast and yeast extract, in other words, by a factor or factors present in the vitamin B_2 complex, factors which are, however, different from both riboflavin and vitamin B_6.

FACTORS IN THE CONTROL OF DENTAL CARIES OF CHILDREN. DR. JULIAN D. BOYD, Iowa City.

A statistical study of repeated dental examinations of over 250 children during ten years serves as a basis for this report. One hundred and seventy-five of these children were under management for diabetes mellitus; 21 were normal, serving as subjects for prolonged metabolic studies; the remainder were under treatment for latent hereditary syphilis. In all, apparent health was the rule. The first two groups received prescribed diets; the remainder were under no dietary supervision.

Of the first group, only 3 children failed to attain control of caries. As to the remainder of the diabetic children, an average period of four years elapsed before further evidences of caries appeared; in 40 per cent there was no evidence of reactivation. In all but 7 of those showing reactivation it remained at minimal levels. The exceptions are explainable on the basis of noncooperation in the prescribed regimen. Of the group of normal children, caries was controlled in all but 3; these children designedly received diets with a suboptimal content of

specific nutritional essentials. Comparison of the rate of appearance of new cavities in the children under dietary control with that observed in the uncontrolled group revealed that residual caries diminished in the former group in the course of years whereas it increased in the latter. Statistical analysis of the data shows these differences to be significant.

Various types of diets have proved effective in arresting caries. These have differed widely in several respects; some were high in fats and some low; some were limited in carbohydrate content, and others supplied the majority of calories in that form. Some effective diets contained preponderant amounts of dextrose. Some were of the usual consistency, whereas others were soft or liquid over periods of months. All were similar, however, in their high content of protective factors. When compared with even the better type of diet prevalently used, the diets effective in prevention of tooth decay are found to offer greater amounts of protein, of lime and of vitamins A, C, D and G. No attempt is made to emphasize the importance of individual factors in protection of teeth; the desirability of general improvement in diet is stressed.

Mouth hygiene was poor in the majority of the subjects; it offered no correlation with the condition of the teeth. Age seems to have been a factor; there was more tendency for caries to advance during the period of rapid growth than at other periods.

It is concluded that intrinsic factors play a preponderant role in the protection of the teeth from decay and that the use of diets which are richer in protective factors than those commonly employed is desirable for the furtherance of optimum nutrition.

DISCUSSION

Dr. Hugh McCulloch, St. Louis: For a long time my associates and I have been interested in dental caries in a group of children in the convalescent department of the St. Louis Children's Hospital. We completely agree with Dr. Boyd that the problem is largely a matter of diet.

This convalescent department is occupied largely by rheumatic children. Most of them were in a poor state of nutrition before arrival, and most of them have marked caries of the teeth.

We regularly observed repair of the type Dr. Boyd has described, both in the primary and in the permanent teeth. These children were subject to no dietary control whatsoever except that they received adequate calories. The two factors which we believe played the greatest part were the consumption of a large amount of fresh milk and the unusual exposure to sunlight. This principle of repair in the teeth probably applies to other body tissues as well.

Book Reviews

Intracranial Tumors of Infancy and Childhood. By Percival Bailey, M.D.; Douglas N. Buchanan, M.D., and Paul C. Bucy, M.D. Price, $5. Pp. 598, with 23 plates. Chicago: University of Chicago Press, 1939.

This excellent book records the results of a clinical and pathologic study of 100 consecutive cases of verified intracranial tumor in infancy and childhood (up to the age of 16 years). The cases are grouped and discussed according to the general location of the tumor and therefore in a manner most valuable for the clinician.

The first 415 pages are devoted to a summary of each of the cases, with history, physical findings, pathologic picture, cause, treatment and, finally, valuable comments on the interesting features. There were 7 cases of ependymoma of the fourth ventricle, 18 cases of malignant tumor of the cerebellum, 25 cases of benign glioma of the cerebellum, 14 cases of glioma of the brain stem, 10 cases of glioma of the optic chiasm, 11 cases of tumor of the cerebral hemispheres, 5 cases of craniopharyngioma, 5 cases of tumor of the pineal body and 5 cases of miscellaneous tumors.

There is a chapter on general symptomatology, again with emphasis on general and localizing manifestations. A chapter is devoted to differential diagnosis, describing 26 cases of suspected tumor which was proved to be some other condition, such as retrobulbar neuritis, thrombosis of the dural sinuses, subtentorial hemorrhage at birth with subsequent adhesions or subdural hemorrhage. Additional chapters are devoted to the general pathology of cerebral tumors and to the technic and results of treatment.

This volume is unusually instructive. The material is presented in an interesting and understandable manner, forming a contribution to the neurology of childhood of interest to every pediatrician.

Appendicitis: A Statistical Study. By Matthew Young and W. T. Russell. Price, 1 shilling net. Pp. 64, with 36 tables. London: His Majesty's Stationery Office, 1939.

This statistical survey of appendicitis contains two sections. The first is based on mortality rates for England, Wales and Germany and on figures for the United States furnished by the Metropolitan Life Insurance Company of New York. The period covered extends in general from 1910 to 1935. Of particular interest to the pediatrician is the change in age distribution. The mortality rates of appendicitis for the ages from 0 to 5 years and for those over 45 years have definitely increased in the last twenty years, though for other ages there has been a considerable decline. Another interesting feature is that the mortality rate of the disease is greatest in the upper social classes and declines progressively with the social grade.

The second section deals with morbidity and case fatality and depends on statistics gathered from hospitals in London, Edinburgh and various cities of the United States. There seems to be definite evidence of increased incidence of the disease. The case fatality for uncomplicated involvement has decreased to between 0.5 and 1.0 per cent, but the fatality for appendicitis with generalized peritonitis remains in general at about 30 per cent. The mortality for localized abscess is around 8 per cent.

The material is presented in an orderly and interesting fashion and will remain a valuable source of reference.

Le syndrome hémorragique du nouveau-né. By H. Jahier. Price, paper 26 francs. Pp. 184, with 13 illustrations. Paris: Masson & Cie, 1939.

This book is a monograph of the series entitled "Medicine and Surgery." It contains a complete discussion of the history, etiology, pathology, forms, diagnosis, prognosis and treatment of the group of diseases designated as the syndrome of hemorrhagic disease of the newborn. Under this term the author

includes all conditions that involve bleeding in the newborn, as cephalatoma, cerebral hemorrhage, various forms of melena and umbilical hemorrhage. This includes conditions with various causes such as syphilis, infection and traumas grouped under one head. The number of reported cases is therefore given as 1 or 2 per hundred instead of 1 in 2,000 or 3,000, as with the usual classification of the condition. However, this point of view is as good as any and is interesting. The work is well done and even though presented in a foreign language is highly readable. The plates are well chosen, and there is a considerable bibliography. It is interesting to note that in the choice of treatment the author advises giving intravenous transfusions instead of wasting time with small intramuscular injections of blood. This volume should prove intensely interesting to any one interested in problems of the newborn.

Biographies of Child Development. By Arnold Gesell, M.D.; Burton M. Castner, Ph.D.; Helen Thompson, Ph.D., and Catherine S. Amatruda, M.D. Price, $3.75. Pp. 328, with 16 illustrations, including 10 graphs, and 33 tables. New York: Paul B. Hoeber, Inc. (Medical Book Department of Harper & Brothers), 1939.

This book describes mental growth, especially intellectual development, with its general and individual variations. Case records are used to illustrate the different aspects and characteristics of growth. "The book assembles concrete studies of individual differences in the patterning of early behavior development."

Part I deals with a group of subjects studied in the Yale Clinic of Child Development and first reported ten years ago. Dr. Gesell reexamined these children. He concluded that the development of most children is predictable during infancy, but in some cases the prognosis made at that time was found to be erroneous. In addition to the case reports there is a summary of the concepts and principles which underlie developmental diagnosis.

Part II continues the individual studies of intellectual growth, especially emphasizing the variations of individual characteristics. Superior mental endowment, language problems, reading disabilities, irregularity in early mental development, immaturity and prematurity, twinship, physical complications and foster care and adoption are considered, with illustrative cases.

The final chapter discusses the individuality of growth curves.

This book is interestingly and plainly written from the clinical point of view. It gives the best description of growth of intelligence which has been published.

Le fragilité osseuse congénitale. By H. Fulconis. Price, paper 28 francs. Pp. 134, with 14 illustrations. Paris: Masson & Cie, 1939.

This excellently written monograph fully discusses congenital fragility of the bones under the headings history, etiology, clinical studies, forms, experimental work, diagnosis, evolution and treatment. The plates are well chosen, and there is a full bibliography. The book is one of the most complete reviews of this unusual condition that I have seen; it should be read by every one interested in the subject.

News and Comment

American Board of Pediatrics.—The American Board of Pediatrics will hold examinations during 1940 as follows: on April 30 and May 1, in New York; before the meeting of Region III of the American Academy of Pediatrics (date indefinite), in Kansas City, Mo., and before the meeting of Region IV of the American Academy of Pediatrics (date indefinite), in Seattle.

Directory of Pediatric Societies*

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Prof. Luigi Spolverini, Policlinico Lungo Tevere Melini 24, Rome, Italy.
Secretary: Professor Vitetti, Rome, Italy.
Place: Boston. Time: Sept. 3-5, 1940.
American Committee:
Chairman: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
General Secretary: Dr. Kenneth D. Blackfan, 300 Longwood Ave., Boston.
Assistant Secretary-Treasurer: Dr. Charles F. McKhann, 300 Longwood Ave., Boston.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

British Paediatric Association

President: Prof. Charles McNeil, 44 Heriot Row, Edinburgh, Scotland.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

Royal Society of Medicine, Section for the Study of Disease in Children

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Sociedad Cubana de Pediatría

President: Dr. Clemente Inclan Costa, Manrique 48, Habana.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Vedado, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

Société de Pédiatrie de Paris

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincaré, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue du Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

NATIONAL

American Medical Association, Scientific Assembly, Section on Pediatrics

Chairman: Dr. Albert D. Kaiser, 16 N. Goodman St., Rochester, N. Y.
Secretary: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Place: New York. Time: June 10-14, 1940.

American Academy of Pediatrics

President: Dr. H. F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Netherland Plaza Hotel, Cincinnati. Time: Nov. 16-18, 1939.
Region I. Place: Mayflower Hotel, Washington, D. C. Time: April 4-6, 1940.
Region II. Place: Edgewater Gulf Hotel, Edgewater Park, Miss. Time: March 22-23, 1940.
Region IV. Place: Seattle, Wash. Time: May 30-June 1, 1940.

American Hospital Association, Children's Hospital Section

Chairman: Miss Mabel Binner, Children's Memorial Hospital, Chicago.
Secretary: Winifred Culbertson, Children's Convalescent Hospital, Cincinnati.

American Pediatric Society

President: Dr. Herbert B. Wilcox, 39 E. 75th St., New York.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid St., St. Louis.

Canadian Society for the Study of Diseases of Children

President: Dr. L. M. Lindsay, 815 Medical Arts Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.

Society for Pediatric Research

President: Dr. Daniel C. Darrow, 330 Cedar St., New Haven, Conn.
Secretary: Dr.Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. R. Cannon Eley, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. Frederick Fischer, 407 Riverside Ave., Spokane, Wash.
Secretary: Dr. C. L. Lyons, Paulsen Medical-Dental Bldg., Spokane, Wash.

Rocky Mountain Pediatric Society

President: Dr. John Schoonover, Republic Bldg., Denver.
Secretary: Dr. F. Craig Johnson, 1850 Gilpin St., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 7:30 p. m.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. Hughes Kennedy Jr., Highland Plaza Apts., Birmingham, Ala.
Secretary: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables, Fla.
Place: Memphis, Tenn. Time: Nov. 21-24, 1939.

STATE

Alabama Pediatric Society

President: Dr. Stewart H. Welch, 1117 S. 20th St., Birmingham.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.

Arkansas State Pediatric Association

Chairman: Dr. G. D. Murphy, 112 Peach St., El Dorado.
Secretary: Dr. Madeline M. Melson, 909 Main St., Little Rock.

California State Medical Society, Section on Pediatrics

Chairman: Dr. Harold K. Faber, 2341 Clay St., San Francisco.
Secretary: Dr. Hartzel H. Ray, 23-2d Ave., San Mateo.

Florida State Pediatric Society

President: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables.
Secretary: Dr. George N. Leonard, 605 Lincoln Rd., Miami Beach.
Place: Concurrent with state association meeting at time of convention.

Georgia Pediatric Society

President: Dr. L. H. Muse, 384 Peachtree St. N. E., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Scientific Meeting: Place: Atlanta. Time: December 1939. Business Meeting: Place: Savannah. Time: April 1940.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. C. V. Calvin, 144 Golden Hill St., Bridgeport.
Secretary: Dr. E. T. Wakeman, 129 Whitney Ave., New Haven.
Time: Three meetings a year.

Indiana State Pediatric Society

President: Dr. O. N. Torian, 23 E. Ohio St., Indianapolis.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Morgan J. Foster, 837 Higley Bldg., Cedar Rapids.
Secretary-Treasurer: Dr. Arnold M. Smythe, 406-6th Ave., Des Moines.

Louisiana State Pediatric Society

President: Dr. Phillip C. De Verges, Audubon Bldg., New Orleans.
Secretary-Treasurer: Dr. W. C. Rivenbark, 220 Physicians and Surgeons Bldg., New Orleans.

MEDICAL SOCIETY OF STATE OF NEW YORK, SECTION ON PEDIATRICS

Chairman: Dr. Paul W. Beaven, 26 S. Goodman St., Rochester.
Secretary: Dr. Leslie O. Ashton, 842 Park Ave., New York.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. John M. Higgins, 600 S. Wilbur Ave., Sayre.
Secretary: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Allan L. Richardson, 3001 W. Grand Blvd., Detroit.
Secretary: Dr. Ward L. Chadwick, 524 Medical Arts Bldg., Grand Rapids.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Guy C. Jarratt, 920 Crawford St., Vicksburg.
Secretary-Treasurer: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Place: To be designated by society. Time: Yearly.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. Herman M. Jahr, 1120 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. Elmer W. Bantin, 440 Aquila Court Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Marion Y. Keith, 369 N. Elm St., Greensboro.
Secretary: Dr. G. W. Kutscher Jr., 176 Woodfin St., Asheville.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. A. L. Salomon, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Ben H. Nicholson, 301 W. 12th St., Oklahoma City.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. D. Lesesne Smith Jr., 187 Oakland Ave., Spartanburg.
Secretary-Treasurer: Dr. William Weston Jr., 1428 Lady St., Columbia.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. William E. Van Order, 546 McCallie Ave., Chattanooga.
Secretary: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.

TEXAS PEDIATRIC SOCIETY

President: T. A. Tumbleson, 2100 North St., Beaumont.
Secretary-Treasurer: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Place: Fort Worth. Time: Oct. 14, 1939.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. W. Ambrose McGee, 616 W. Grace St., Richmond.
Secretary: Dr. John M. Bishop, Medical Arts Bldg., Roanoke.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. J. L. Blanton, 207 Fairmont Ave., Fairmont.
Secretary: Dr. Theresa O. Snaith, 450 Center Ave., Weston.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. N. C. Wetzel, 2103 Adelbert Rd., Cleveland.
Secretary: Dr. Fred Rittenger, 10515 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. T. B. Verner, 170 St. George St., Toronto, Canada.
Secretary: Dr. D. V. Hutton, 170 St. George St., Toronto, Canada.

BRONX PEDIATRIC SOCIETY

President: Dr. Samuel T. Levethan, 254 E. 184th St., Grand Concourse, New York.
Secretary: Dr. David Greene, 910 Grand Concourse, New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. Benjamin Kramer, 6 Pierrepont St., Brooklyn.
Secretary: Dr. John A. Monfort, 861 Carroll St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, July, August and September.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. Frank van der Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Thursday of April and September.

CHICAGO PEDIATRIC SOCIETY

President: Dr. Gerard N. Krost, 2376 E. 71st St., Chicago.
Secretary: Dr. George F. Munns, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

DALLAS PEDIATRIC SOCIETY

President: Dr. Harold Nesbit, 1719 Pacific Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

DETROIT PEDIATRIC SOCIETY

President: Dr. William O'Donnell, 1553 Woodward Ave., Detroit.
Secretary: Dr. Robert Mason, 5140–2d Blvd., Detroit.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

FULTON COUNTY MEDICAL SOCIETY, PEDIATRIC SECTION (ATLANTA, GA.)

Chairman: Dr. L. H. Goldsmith, 384 Peachtree St. N. E., Atlanta.
Secretary: Dr. James P. Hanner, 384 Peachtree St. N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

HOUSTON PEDIATRIC SOCIETY

President: Dr. James H. Park Jr., 3717 Main St., Houston, Texas.
Secretary-Treasurer: Dr. Thomas J. Donovan, 2418 Travis St., Houston, Texas.
Place: Houston Club. Time: Third Monday of each month.

KANSAS CITY (MISSOURI) PEDIATRIC SOCIETY

President: Dr. Urban Busiek, 200 E. Pershing St., Springfield, Mo.
Secretary: Dr. Fred Speer, 2700 Parallel Ave., Kansas City, Kan.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. H. R. Cooder, 3875 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Paul M. Hamilton, 248 E. Main St., Alhambra, Calif.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd.
Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Benjamin Stoloff, 1149 Eastern Parkway, Brooklyn.
Secretary: Dr. Harry Apfel, 988 Park Pl., Brooklyn, N. Y.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., second Monday of each month, October to March, inclusive.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. James Dobbins, 42-04 Ditmars Blvd., Long Island City, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. Harry H. Donnally, 1612 I St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. Harry A. Spigel, 2647 Connecticut Ave. N. W., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of October, January, February, March and April.

Memphis Pediatric Society

President: Dr. Barton Etter, 376 S. Bellevue St., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

Milwaukee Pediatric Society

President: Dr. Helen Jane Zillmer, 781 N. Jefferson St., Milwaukee.
Secretary-Treasurer: Dr. Samuel E. Kohn, 425 E. Wisconsin Ave., Milwaukee.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Philip M. Stimson, 25 Claremont Ave., New York.
Secretary: Dr. Lucy Porter Sutton, 168 E. 74th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

Northwestern Pediatric Society

President: Dr. Robert Rosenthal, 437 Lowry Medical Arts Bldg., St. Paul.
Secretary-Treasurer: Dr. R. E. Nutting, 205 W. 2d St., Duluth, Minn.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Oklahoma City Pediatric Society

President: Dr. A. L. Salomon, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Time: Every month, except June, July and August.

Philadelphia Pediatric Society

President: Dr. Samuel Goldberg, 4546 N. Broad St., Philadelphia.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

Pittsburgh Pediatric Society

President: Dr. James LeRoy Foster, Highland Bldg., Pittsburgh.
Secretary-Treasurer: Dr. E. R. McClusky, 3200–5th Ave., Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

Richmond Pediatric Society

President: Dr. Emily Gardner, 1100 W. Franklin St., Richmond, Va.
Secretary-Treasurer: Dr. T. Stanley Meade, 913 Floyd Ave., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., first Thursday of each month, except July, August and September.

Rochester Pediatric Society

President: Dr. David Wolin, 16 N. Goodman St., Rochester, N. Y.
Secretary: Dr. H. C. Soule, 16 N. Goodman St., Rochester, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Second Friday of each month.

St. Louis Pediatric Society

President: Dr. Ralph L. Cook, 508 N. Grand Blvd., St. Louis.
Secretary-Treasurer: Dr. Peter G. Danis, 634 N. Grand Blvd., St. Louis.
Place: St. Louis Medical Society Bldg. Time: Third Friday of each month from September to June.

Seattle Pediatric Society

President: Dr. Jay I. Durand, 1305–4th Ave., Seattle.
Secretary: Dr. Frederick B. Joy, 1215–4th Ave., Seattle.
Place: College Club. Time: Third Friday of each month, 6:30 p. m.

Southwestern Pediatric Society

President: Dr. E. Earl Moody, 829 S. Alvarado Ave., Los Angeles.
Secretary: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Clement Smith, 1101 Beacon St., Brookline, Mass.
Secretary: Dr. D. Murray Cowie, University of Michigan, Ann Arbor, Mich.

Westchester County Medical Society, Pediatric Section (New York)

President: Dr. Norman Survis, 650 Main St., New Rochelle.
Secretary-Treasurer: Dr. Elvira Ostlund, 131 Purchase St., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.